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STATE OF THE SYSTEM OF HEMOSTASIS, FIBRINOLYSIS AND MICROCIRCULATION HEART DISEASE

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The book presents the results of population-genetic, prospective studies of coronary artery disease, taking into account both the main risk factors and previously unstudied ones in the form of disorders in the systems of hemostasis, fibrinolysis and microcirculation.

The data obtained as a result of studies indicating a significant role of changes in hemocoagulation and microcirculation in the occurrence and development of CHD are presented. It has been shown that some indicators of microcirculation and hemocoagulation are predictors of heart disease.

Based on a large amount of factual material, data on the prevalence of CHD and its main risk factors among the population, their relationship with disorders in the hemocoagulation and microcirculatory systems are presented.

Separate chapters are devoted to the prognostic value, the combined influence of individual risk factors on the development of coronary artery disease, the study of family relationships of these indicators, as well as the multifactorial analysis of the study results.

The characteristics of the systems of hemostasis, fibrinolysis and microcirculation in normal and pathological conditions are also presented.

Recommendations for practical health care are given.

The book is intended for cardiologists, medical school professors, residents, students and a wide range of doctors.

LIST OF ABBREVIATIONS

AH – Arterial hypertension

BFI – Blood flow index

BMI – Body mass index

CHD – Coronary heart disease

CI – Composite index

DIC – Disseminated intravascular coagulation

DLP – Dyslipoproteinemia

FAI – Peariascular fat attenuation index

FG – Fibrinogen

FN - Fibronectin

FDPs – Fibrinogen degradation products

FDPs (IH) – FDPs (immunochemical method)

HLP – Hyperlipidemia

HCH - Hypercholesterolemia

HT – Free heparin time

MC – Microcirculation

MCB – Microcirculatory bed

PT – Prothrombin index

SF – Soluble fibrin

TG – Triglycerides

TT – Thrombin time

CH – Cholesterol

CH – HDL – High-density cholesterol lipoproteins

CH – LDL – Cholesterol – low-density lipoproteins

INTRODUCTION

Relevance of the problem. In recent years, the intensive development of cardiology and hemostasiology has made it possible to clarify and concretize the role of formed elements, primarily platelets and erythrocytes, plasma factors and fibrinolysis in the pathogenesis and formation of various forms of coronary heart disease (CHD) and circulatory disorders.

Cardiovascular diseases (CVDs) represent a major proportion of chronic pathology and mortality in industrialized countries and are emerging as an important public health problem in developing countries. CHD is the most common cause of death in most countries around the world.

It should be noted that in recent years, the incidence of CHD and mortality among young people has also increased.

Over the past decades, experience has been gained in the fight against CHD with the use of numerous preventive measures.

However, despite this, the incidence and mortality of CHD are still high.

The above makes the issue of CHD prevention and related problems, in the form of studying risk factors at the preclinical stage, developing effective measures to reduce morbidity, a primary task. One of the ways to solve this important problem is the prevention of a comprehensive, multifactorial assessment of CHD risk factors, which is carried out in different regions of the country, among the population of different ethnic groups.

Numerous clinical studies have established the important role of hypercoagulation, depression, fibrinolysis, platelet disorders and lipid metabolism in the pathogenesis of atherosclerosis and coronary artery disease. Changes in the indicators of the blood coagulation and anticoagulation systems in atherosclerosis, coronary artery disease, and coronary atherosclerosis have been studied quite well. A lot of data has been obtained as a result of biochemical and pharmacological study of physiologically active substances formed in the tissues of the inflammatory focus and playing an important role in the physiological regulation of the microcirculatory bed. At present, it has become possible, by means of a comprehensive study of hemostasis, to assess not only the general direction of changes in the direction of both hyper- and hypocoagulation, but also to catch increased intravascular coagulation of a latent nature, which, as is known, plays the role of a trigger mechanism for atherosclerosis in subsequent thrombotic complications. At the same time, the effect of pharmacological substances on microcirculation was also studied. Many clinical observations have been carried out in various diseases, for example, in heart attack, atherosclerosis, rheumatism, diabetes, surgical interventions, heart surgery, traumatic shock, etc.

But despite this, the interest of various medical specialties in the study of the patterns of intravascular thrombosis and microcirculation has increased significantly. This can be explained by the fact that, as we know, the microvascular bed is the place where, as a result, the transport function of the cardiovascular system is realized and transcapillary exchange is ensured, creating the tissue homeostasis necessary for life. Also, the importance of this problem lies in the fact that it covers many interrelated and interdependent processes: the laws of blood and lymph circulation, the patterns of blood cell behavior (deformation, aggregation, adhesion, etc.), the patterns of blood coagulation (coagulation, fibrinolysis, thrombosis, the role of platelets), the laws of transcapillary metabolism and ultrastructural features both in normal conditions and in various types of pathology. For example, in case of cardiovascular pathology, tissue damage, radiation, inflammatory processes, exposure to infectious and toxic agents, disorders of the blood coagulation system, neoplasms, metastasis, various types of traumatic, blood transfusion, anaphylactic, cardiogenic shock.

As mentioned above, the problem of disorders in the microcirculatory bed concerns all branches of medicine, so, for example, a deep study of this problem will make it possible to make a huge step in transplant surgery, resuscitation, therapy, oncology, and space medicine.
The study of the problem of microcirculation, fibrinolysis and hemostasis is of great practical importance. In particular, first of all, in the prevention and treatment of regional disorders: coronary, cerebral, renal and hepatic circulation, general circulatory insufficiency, various types of shock. For example, in cardiogenic shock: rapid change of hypercoagulation and increase in the adhesive-aggregation capacity of platelets of hypocoagulation with increased thrombocytopenia and thrombocytopathy, a decrease in the activity and content of procoagulants and spontaneous fibrinolysis. Also, in the development of atherosclerosis, along with the dominant role of lipoproteins, they began to attach importance to damage to the vascular wall, aggregation of platelets, erythrocytes and exposure of fibronectin, release of proliferating factor from platelets, depletion of prostrocyclin infiltrating it with fibrinogen. The role of thrombosis and spasm in the occurrence of angina pectoris, along with reversible platelet blockage and coronary spasm due to the release of thromboxane and serotonin from platelets is being studied.

We conducted a study to study one of the most pressing problems of cardiology – disorders in the system of hemostasis, fibrinolysis and microcirculation in CHD and in its preclinical stage. The relevance of this problem for modern health care is undeniable, as it is due to the prevalence of coronary artery disease, high mortality, and large labor losses, both from temporary disability and early disability.

Numerous clinical and experimental studies confirm the role of changes in the blood coagulation and anticoagulation system in the pathogenesis of CHD, as well as an autoimmune disorder in the development of both the disease itself and its main risk factors.

At the same time, there are insufficient population studies to study the role of the disorder in the systems of hemocoagulation, fibrinolysis and microcirculation, at the same time, without taking them into account, it is not possible to obtain an objective comprehensive assessment of the epidemiological situation with regard to CHD in the population.

At present, it has become possible, through a comprehensive study of hemostasis, to assess not only the general direction of changes in the direction of both hyper- and hypocoagulation, but also to catch increased intravascular coagulation of a latent nature, which, as is known, plays the role of a trigger mechanism for atherosclerosis and other subsequent thrombotic complications.

Studies of the system of hemostasis, fibrinolysis, blood rheology and microcirculation system in patients with CHD confirmed the presence of hypercoagulable disorders, an increase in blood viscosity, and a violation of its aggregant state. It is known that changes in microcirculation and hemostasis, fibrinolysis, and blood rheology occur in parallel in the early stages of CHD and progress as the severity increases. The emergence of methodological approaches to the study of microcirculatory bed (MCB) has made it possible to significantly expand the understanding of changes in the vascular wall and clarify their significance in the pathogenesis of coronary artery disease.

For the genetic analysis of the structure of CHD predisposition, it was necessary to carry out, in addition to lipid metabolism and hypertension indicators, a comprehensive genetic analysis of hemocoagulation and microcirculation indicators, since it is known that there is a connection between them and coronary artery disease.

There is evidence of the role of hyperurecemia and pesticemia as a factor in the development of coronary artery disease.

It has been established that heredity is also one of the factors that are important in the pathogenesis of coronary artery disease.

It is known that both CHD itself and its risk factors tend to familial concentration, and for variables such as blood lipids, glucose tolerance, blood pressure, etc., there are significant correlations between relatives. All this suggests a possible role of hereditary factors that determine the variation of these quantitative traits in the realization of a predisposition to coronary artery disease. A modern approach to the study of hereditary predisposition to atherosclerosis and CHD is to search for their relationship with genetic markers of blood. The

Mendeleev nature of the inheritance of genetic markers, as well as the qualitative constancy throughout a person's life, allows us to consider them a unique tool for understanding the hereditary predisposition of a person to diseases, including cardiovascular ones. The study of the structure of predisposition to CHD, taking into account the above factors in a particular population, is the basis for planning preventive and therapeutic measures in the population as a whole. Such an integrated approach and population-genetic analysis, especially if it is carried out in a prospective aspect, will make it possible to find out the preclinical signs of the disease, and possibly to determine the markers.

Clarification of the role of genetically determined signs of the development of CHD and its risk factors, as well as their interrelation, can also lead to the knowledge of the material substat of a person's hereditary predisposition to CHD, which could open up new ways to prevent this disease.

Genetic analysis of CHD risk factors makes it possible to quantify the structure of associations observed in the process of epidemiological studies and to detect the existence of hidden interactions between factors.

Population-based studies conducted in the Fergana valley in recent years indicate an increase in the prevalence of CHD and its risk factors. Based on the studies, along with other factors, special attention should be paid to other possible etiological factors, in particular, an increase in blood clotting capacity, deterioration of blood supply at the microvascular level, physical inactivity, etc.

This monograph presents the concept of microcirculation, hemostasis and fibrinolysis in normal and pathological conditions, in particular in coronary artery disease.

This information will allow you to understand the processes occurring in the human body, will serve as an incentive for further study of them, which will help to solve many problems that are based on a violation of microcirculation and coagulation properties of blood.

UNDERSTANDING MICROCIRCULATION, HEMOSTASIS AND FIBRINOLYSIS SYSTEMS

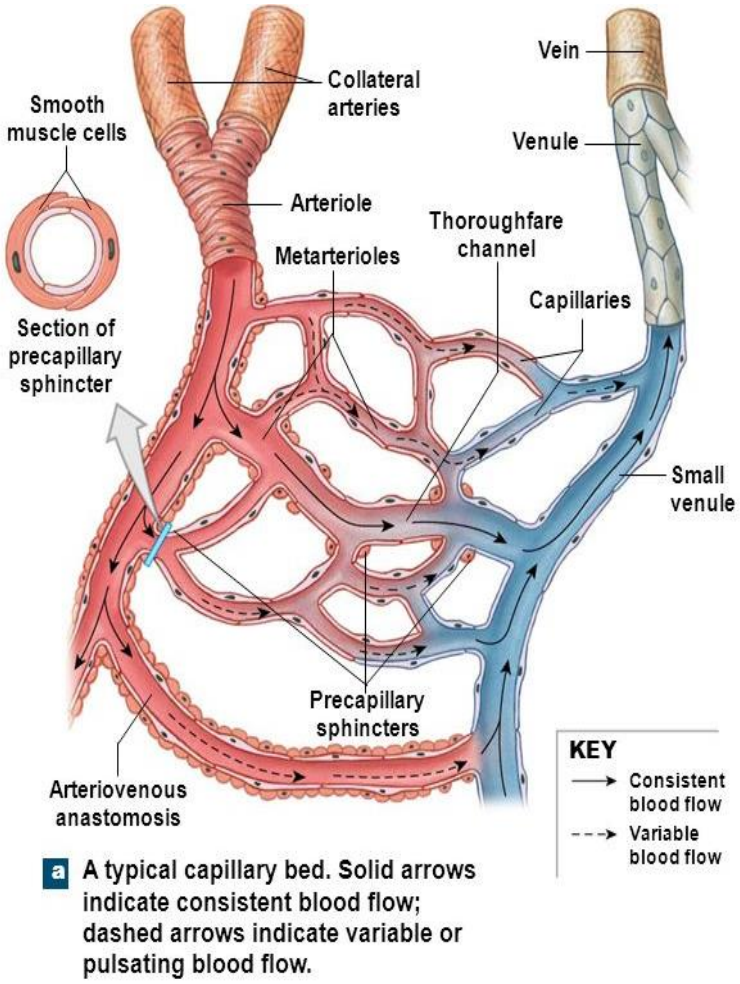
THE CONCEPT OF MICROCIRCULATION

What is microcirculation?

The problem of microcirculation is being actively developed all over the world.

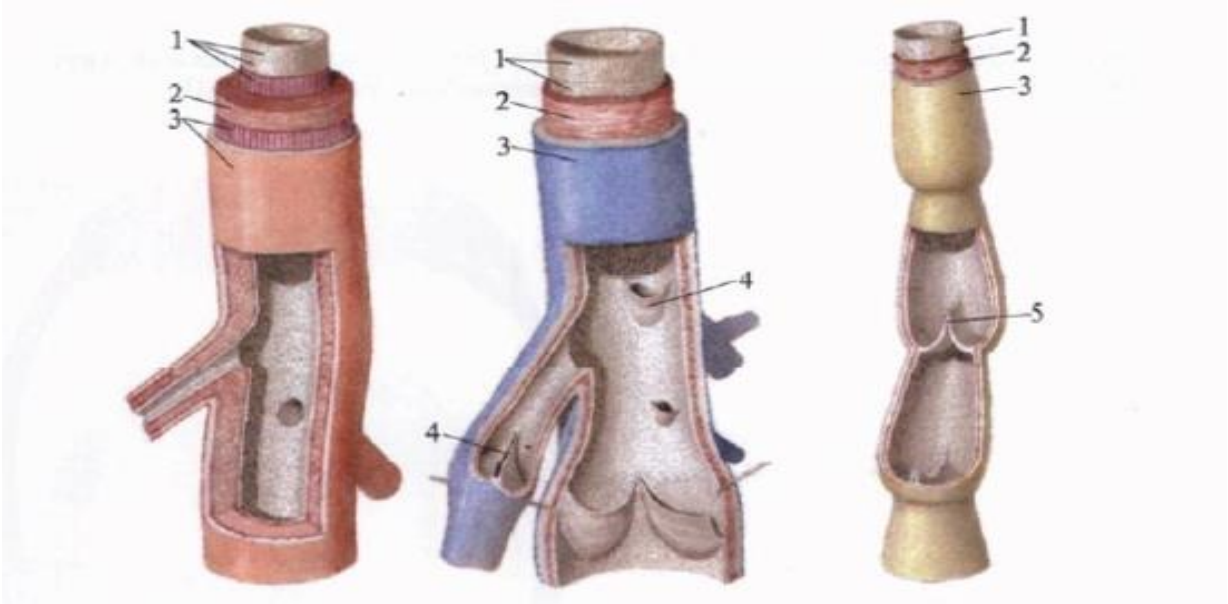
The vascular system is a system of tubes through which, through the fluids circulating in them (blood and lymph), on the one hand, the necessary nutrients are delivered to the cells and tissues of the body, and on the other hand, the waste products of cellular elements are removed and these products are transferred to the excretory organs (kidneys).

According to the nature of the circulating fluid, the vascular system is divided into: 1) the circulatory system, the system of tubes through which blood circulates (arteries, veins, sections of the microcirculatory bed, and the heart), and 2) the lymphatic system, a system of tubes that move colorless fluid, the lymph [1,5].



Picture. 1 Links of the microcirculatory bed:

Microcirculation is a collective term. Words ***Microcirculation*** It originated from the Greek word mikros, which means small + the Latin word circulatio means rotation and means the transport of biological fluids at the level of body tissues: the movement of blood through capillary microvessels (capillary circulation), the movement of interstitial fluid and substances through the intercellular spaces and the transport of lymph through the lymphatic microvessels. The term was introduced by American researchers in 1954 in order to integrate methodological approaches and information that related mainly to capillary blood flow [24].



Picture. 2 Structure of the artery wall (A), vein (B) and lymphatic vessel C (diagram)
1. tunica intina;
2. tunica media;
3. tunica externa;
4. valvula venosa;
5. lymphatic Valve

The development of this direction has led to the idea of microcirculation as a a complex system that integrates the activity of three subsystems: hemomicrocirculatory, lymphocirculatory and interstitial. Microcirculation gets its name from the microsize of the vessels involved in it. The MCB consists of vessels with a diameter of less than 100 μm. which are only visible under a microscope. Human aging involves different functions performed by different organs. But the performance of the function requires constant regulation of the nutrition of these organs and systems. ensuring trophic, respiratory, excretory, regulatory functions of the vascular system, the development of inflammatory and immune reactions. According to V. V. Kupriyanov, it includes 5 links: 1*) arterioles as the most distal links of the arterial system, 2) precapillaries, or precapillary arterioles,* which are an intermediate link between arterioles and true capillaries; 3) capillaries; (4*) postcapillaries, or postcapillary venules, and* (5) *venules,*

which are the roots of the venous system. The process of microcirculation of fluid is not limited to microscopic blood vessels. The human body consists of 70% water, which is contained in cells and tissues and makes up the bulk of blood and lymph. Only 1/5 of all fluid is in vessels, and the remaining 4/5 of it is contained in cell plasma and in the intercellular environment. Microcirculation of fluid In addition to the circulatory system, it is also carried out in tissues, in serous and other cavities and on the lymph transport route. The main task of the microcirculation system in the body is to maintain a dynamic equilibrium of volumetric and mass parameters of fluid and substances in tissues, i.e. to ensure homeostasis of the internal environment. The microcirculation system carries out the transport of blood and lymph through microvessels, the transport of gases, water, micro- and macromolecules through biological barriers (capillary walls) and the movement of substances in the extravascular space.

The velocity of blood flow in the capillaries is low and amounts to 0.5-1 mm/s. Thus, each particle of blood stays in the capillary for about 1 s. The small thickness of the blood layer (7-8 μm) and its close contact with the cells of organs and tissues, as well as the continuous change of blood in the capillaries, provide the possibility of exchange of substances between the blood and the tissue (intercellular) fluid, tissues. The number of capillaries per 1 mm2 of cross-section is greater than in tissues with less intensive metabolism.

After overcoming the barrier in the form of a capillary wall, substances enter the perivascular space. What is their further fate?

The study of the ultrastructure of organs and tissues has shown that an important role is given to the unequal role of the perivascular space and interstitial tissue in the organization of hemato-tissue metabolism. This disparity is determined by the difference in the spatial relationships between specialized tissue cells and microvessels. For example, in the liver, liver cells have almost direct contact with blood plasma, and the penetration of substances from the blood into the bile capillaries depends not on the permeability of the intra-organ connective tissue, but on the density of contacts between the liver cells themselves. In connective tissue-rich organs, the relationship between blood microvessels and specialized cells becomes much more complex, albeit to varying degrees. In skeletal muscle, for example, the capillary "works" directly on the muscle fiber with one side and predominantly on the interstitium with the other. But even in the first case, there is often not a homogeneous medium between the capillary wall and the fiber, but a highly structured system of various fibrillar elements immersed in a homogeneous matrix [1,5,7].

CAPILLARY PERMEABILITY AND ULTRASTRUCTURAL MECHANISMS OF TRANSCAPILLARY EXCHANGE

In the mechanisms of tissue homeostasis, one of the most important places is occupied by the exchange of substances between the blood and the interstitial environment, i.e., the blood-tissue, or transcapillary, exchange. This exchange between the blood and the interstitial medium is carried out through the wall of capillary microvessels: arterial and venous capillaries, post-capillary venules. It depends, on the one hand, on the permeability of the vascular wall, on the size of the capillary surface (filtration area), and on the other hand, on hemodynamic and osmotic factors. It is known, for example, that the diffusion transport of substances from the blood to the tissue can increase by a factor of 8 with an increase in the volumetric velocity of capillary blood flow (Renkin, 1968). Moreover, hemodinum shifts, which lead to an increase in capillary pressure, can also affect the qualitative indicators of exchange between blood and tissues. Thus, an experimental increase in venous pressure leads to an increase in transcapillary transport of macromolecules and a simultaneous decrease in the transport of micromolecules (Arturson, 1972). There is no doubt that the qualitative and quantitative characteristics of blood-tissue metabolism also depend on the processes that take place on the other side of the capillary wall and determine various concentration gradients. Therefore, the analysis of the mechanisms of transcapillary metabolism and, moreover, the clarification of the causes of its disorder, as well as the assessment of the role of these disorders in tissue pathology, for example, in the development of edema, should always take into account all factors. But in any case, the focus is on the capillary wall with its specialized function of connecting and delimiting adjacent media, which is based on a common property of biological barriers, namely selective permeability [1,6, 11,12,17].

DIFFUSION AND ULTRAFILTRATION

It is now known that metabolism through the capillary wall is carried out on the basis of ultrafiltration and diffusion, as well as microvesicular transport. Landis (1927–1964), which has now become a classic, demonstrated the importance of capillary filtration using the method of biomicroscopy. Filtration is the penetration of a substance of a certain molecular weight through a certain size of pores in a membrane under the influence of hydrostatic pressure or towards increased osmotic pressure. The capillary filtration coefficient expresses the amount of fluid that is filtered through a certain area of the vessel wall per unit of time at a certain blood pressure. Direct measurement of blood pressure in capillaries using a microcannula, provided materials to substantiate Starling's hypothesis on the filtration

mechanism of permeability, according to which the exchange of fluid between blood and tissue is determined by the difference between hydrostatic and colloid-osmotic pressure, both at the arterial and venous areas of the capillary. At hydrostatic pressure of 9.5-12.5 cm of water. Filtration stops, and at a pressure of 5 cm of water. Absorption occurs, i.e., fluid enters the capillary at a rate of 0.02–0.05 μm3/μm2 per second. Equilibrium is established at waters. When the hydrostatic and colloidal-osmotic pressures are equal. If the hydrostatic pressure is higher than this value, filtration takes place, if it is lower, absorption takes place. It is believed that the hydrostatic pressure in the capillaries is due to the activity of the precapillary sphincter. When it is closed, the hydrostatic pressure decreases, but the absorption pressure increases, as a result of which the passage of tissue fluid into the capillaries increases. When the sphincter opens, the hydrostatic pressure increases, the number of active capillaries and the area of capillaries through which filtration is carried out increases. Thus, the transcapillary exchange of fluid depends on the rate of vasomotion and on the duration of the predominant phase. It is clear that ultrafiltration depends not only on the filtration pressure, but also on the state of the ultrafilter, such as the capillary wall. At the same time, only those molecules whose size does not exceed the size of the pores of the ultrafilter are transferred through the wall with the fluid flow. In another mechanism of transcapillary exchange, namely diffusion, substances pass from one medium to another (from blood to tissue and vice versa) regardless of the presence of fluid by the flow, but due to the existence of concentration gradients of these substances on both sides of the capillary wall and the presence of a continuous aqueous phase in which they are distributed in accordance with the laws of thermodynamics [1,6, 11,12,17].

Diffusion is the mutual penetration of contiguous substances towards each other in the direction of decreasing their concentration, ultimately for the uniform distribution of diffusing substances throughout the space where these substances are located. In the case of simple (free) diffusion, molecules and ions move freely in the direction of their decreasing concentration (e.g., small molecules such as gas and water, and simple chemicals soluble in the latter). In the case of a lighter Diffusion molecules and ions can move even in the case of various difficulties with the help of molecules of other "carrier" substances. Of significant importance in the mechanisms of transcapillary metabolism, as already noted, is the component of diffusion of various low-molecular-weight substances and gases soluble in water and fats directly through the endothelial cell, since it is known that the latter is permeable to these substances. Capillary permeability to solutions by diffusion (Renkin 1971) can be determined using Fick's rule expressed by the following formula:— dn/dt = ps-Ac, *where* -dn/dt *is the diffusion rate; Ac* is the difference in the concentration of solutions on both sides of the capillary wall.

Disruption of diffusion processes plays a significant role in transcapillary metabolism disorders. It should be borne in mind that the exchange of solutions between capillary blood and tissues depends on concentration gradients along the capillary, through its wall and with the surrounding tissue. In essence, these gradients carry out the kinetics of the transport of substances diffusing through the capillary wall. The gradient along the capillary expresses the ratio of diffusion and blood flow. Consequently, disorders of the latter can affect transcapillary metabolism. For capillaries that are surrounded by a well-exchanging medium, the following relationships take place (Renkin, 1971):

$$E = l - exp*(-PS/Q), \quad C = QJ = Q[1 - exp*(- PS/Q)].$$

Herewith E — fractional equation of solution passage through a single capillary; $With$ – capillary clearance of the solution; Q – the amount of blood flow; PS is the product of the capillary permeability of the solution (R) on the effective surface of the endothelial lining of the capillary wall (S). Transport from blood to tissues may be restricted by blood flow $\{C = Q)$. if PS/Q is too large. Diffusion is limited $(C = PS)$, if PS/Q represents a small value. In the capillaries of some tissues (e.g., cardiac or striated muscle), the exchange of water and fat-soluble substances with low molecular weight is quite limited by the amount of blood flow. The exchange of ions and uncharged molecules insoluble in fats is also restricted. For substances insoluble in fats, permeability (R) decreases as the molecular weight increases. Effective surface of the endothelial lining of the capillary (S) It can be very different depending on the number of open capillaries and is largely determined by vasomotor regulation. If the blood flow is accelerated, then PS has a tendency to build. It should be noted that substances insoluble in fats, which have a molecular weight greater than that of serum albumin, pass by ultrafiltration (usually through interendothelial spaces). Under normal conditions, the transport of large molecules through the capillary wall is very slow compared to water and small molecules. It should also be noted that the diffusion gradient between the blood inside the capillary and the surrounding tissues usually includes not only the connective tissue, but also the lymphatic vessels, but also the parenchymal cells of the organ. In this regard, when assessing the diffusion of substances that penetrate from the capillary into these cells, the diffusion characteristics of the membranes of these cells should also be taken into account. Even for substances that penetrate only into the interstitial extravascular tissues, the mucopolysaccharides of the latter may be factors limiting the spread (diffusion) of the substance from the capillary into these tissues. It

should also be noted that it is important to take into account the gradients that ensure the supply of oxygen to the tissues. The magnitude of these gradients depends on the amount of oxygen absorbed by the respective tissues. At high absorption values, tissue pH can drop to zero in the middle of the distances between the capillaries. At the same time, the rate of diffusion of OG increases due to its absorption by tissues. In muscle, the amount of oxygen uptake depends on the number of open capillaries (Renkin 1971). All of the above concerns the mechanisms of the so-called passive diffusion of substances due to the gradient of their concentrations. However, quite often there is a movement of substances against the concentration gradient, by the so-called active transfer of molecules. It is believed that cell membranes contain enzymes called permeases, which combine with substances that penetrate through the membrane into the cell, and by forming a complex, facilitate their entry into the cell. On the inner surface of the membrane or inside the cell, the permeases are cleaved and the substance ends up in the cell. Clearly, energy is needed for such a process. One of the enzymes that catalyze the reactions associated with the release of energy is the ATPase of the plasma envelope, which is considered to be a component of the enzymatic system responsible for the active transfer of Na and K cells across the membranes. It should only be borne in mind that the difference between the latter and any parenchymal cell is its transport function. Transport enzymes must allow entry and exit from the endothelial cell. This question is almost completely unexplored in relation to the endothelial capillary cell. Perhaps this is due to methodological difficulties. Apparently, this is the reason for the lack of work on enzymopathology of the capillary endothelial cell. However, there are histochemical and electron microscopic studies which are of undoubted interest in this respect. For example, Landers et al. (1962) studied the enzymatic activity of the endothelium and pericytes of cerebral capillaries and found intense activity of ATP-ase, alkaline phosphatase, and diphosphopyridine pucleotide-diaphorase. The localization of ATPase, as noted by Marchesi and Bernett (1964), in endothelial microvesicles suggests that these formations appear to be related to the mechanisms of active transport of substances through the capillary endothelial cell. Different sections of the microvasculature have different permeability. For example, a highly diffusing dye (patent blue V) comes out at the arterial end of the capillary and then in the venous region. Trypan red, which is difficult to diffuse, first appears in the form of a cloud of paint in the venous part of the capillary. The middle position is occupied by bromophenol blue, which appears first in the venous region and then spreads rapidly proximally throughout the capillary bed (Rous E. A., 1930; Rous, Smith, 1931). The described patterns of color diffusion are not significantly affected by such influences as an increase in blood pressure (adrenaline injection), a decrease in systemic pressure to 30 mm Hg. (traumatic shock). The dynamics of the passage

of paints, large molecules, and cells through the endothelial cell using television photometry was also studied. The use of monochromatic light, large light-optical (X90 lens) and electro-optical (TV camera) magnifications made it possible to clearly distinguish the details of the endothelial cell, its membrane, nucleus and nucleolus. The study was conducted on the mesentery, lungs, liver and kidneys of frogs, mice, rats and rabbits (Bloch and Cojas 1964). The authors used isotonic solutions of trypan blue, Evans blue, and acid blue 48. Experiments have shown that particles with a diameter of less than 1 μm, as well as erythrocytes (spontaneous diapedesis in frogs), are able to pass through endothelial cells. Early work on luminescence microscopy on rabbit mesentery showed that fluorochromes such as insoluble esculin (coumarin derivative) and uranine (the sodium salt of fluorescein) behave differently when administered intravenously (1-2 ml of a 1-2% solution). Low-molecular-weight esculin, which does not bind to plasma proteins, leaves the bloodstream as soon as it reaches the capillary, and uranin, which binds to proteins, leaves the venous part of the capillaries, in the venules and small veins (Praff and Herold, 1937). These data show that substances diffuse or filter depending on their properties (molecular size, solubility, etc.) and their ability to bind to plasma proteins. With the help of the luminescent technique in vivid, it was shown that the permeability of the capillary wall in the mesentery of rats increases when substances that change the coagulation function of the blood, such as trypsin, heparin, thrombin, and the anticoagulant marcumar, are introduced into the blood (Witte, I960, 1965). The authors showed an increase in the passage of fluorochrome protein through the walls of venules and small collecting venules, and the development of erythrocyte diapedesis, which is due to a sharp decrease in prothrombin activity (by 95%), and not thrombocytopenia, since the number of platelets did not change. These experiments, according to the authors, indicate the presence of a periendothelial layer of fibrin and confirm the Copley concept. According to this concept, a dynamic equilibrium is established in the intact endothelial wall between the enzymes that form the fibrin-like parietal layer and the fibrinolytic enzymes. When this equilibrium is disturbed in the direction of the predominance of fibrinolysis, the permeability of the vessel wall increases (Daniclli, Stock, 1944; Astrup, 1956; lensen, 1956; Mailer, 1961, 1969; Copley, 1967). These data, indicating the existence of a periendothelial layer of adsorbed plasma proteins, in particular fibrin, suggest that this layer plays an important role in the regulation of vascular permeability and in the mechanisms of penetration of substances through the capillary wall. It is with this layer that substances must interact at the very beginning of their penetration through the capillary wall by diffusion or ultrafiltration. Physiological studies of the distribution of various substances between the blood and the organs quickly led to the conclusion that there are marked differences in the accumulation of the same substances in different organs. This fact has

been interpreted as evidence of organ differences in the permeability of blood vessels. Subsequent numerous studies have shown that such an interpretation is permissible only in relation to macromolecular compounds, and even then taking into account differences in the sorptional capacity of tissues, the rates of lymph formation, and the direct return of indicator substances to the bloodstream (through venous microvessels). More convincing data in favor of the existence of an organ gradient of vascular permeability were obtained in experiments where the dependence of the velocity of the passage of substances in the blood-lymph direction on their molecular size was studied. Three degrees of dependence have been identified: high (in the muscles), medium (in the intestinal wall) and low (in the liver) (Mayerson S. A., 1960; Arturson, 1972 et al.). The permeability of the vessels here is inversely proportional to this dependence. In general, physiological data convincingly prove the existence of an organ gradient of vascular permeability and make it possible to distinguish three groups of organs on this basis: a) organs with relatively low permeability (muscles, heart, lungs, brain, nerves, skin), b) organs with relatively high vascular permeability (liver, spleen, bone marrow), and c) organs occupying an intermediate position in their vascular permeability (intestines, kidneys, endocrine glands). The use of the method of intravital study of the permeability of microvessels for various dyes has shown that macromolecular or micromolecular dyes bound to plasma proteins leave the bloodstream at the level of venous capillaries and postcapillary venules (Rous E. A., 1930; Smith, 1931; Landis, 1946, 1964; Wiederhielm, 1966, 1968; Intaglietta, 1967; Hauck, 1969; Hauck and Schroer, 1969, et al.). In this regard, an interesting observation was made by Zimmerman (1923), who extensively studied the structure and function of pericytes with a light microscope. According to his data, the release of dyes from microvessels occurs in those areas where pericytes are directly located. This observation led him to conclude that pericytes are related to the diffusion of substances through the wall of microvessels. Unfortunately, this observation has been neglected in recent studies, although the issue seems important for understanding the function of pericytes and the mechanisms of transcapillary exchange, as well as for elucidating the causes underlying the "capillary permeability gradient". Thus, in addition to the organ gradient of vascular permeability, there is a gradient of capillary permeability, which is understood as a higher permeability (for macromolecules) of the venous portions of capillary microvessels. The use of macromolecular indicators with different molecular weights led to another important physiological generalization, namely the creation of the "pore theory" (Rarrep-lieimer, 1951; Pappenheimer, 1953; Grotte, 1956; Mayerson, E. A., 1960; Landis, Pappenheimer, 1963; Renkin, 1964; Winne, 1965; Wiederhielm, 1968; Arturson e. a., 1972). This concept is based on the fact that substances with a molecular weight of up to 5000 (effective

radius of 1.5 nm) do not experience significant restrictions in their passage from the blood to the lymph, whereas with a further increase in the size of molecules up to the size of serum albumin (molecular weight 69,000, effective radius 3.5 nm), there is a limitation that increases especially rapidly in the molecular weight range of 15,000–30,000. Accordingly, the ratio of concentrations of these substances in lymph and blood drops sharply, from 1 (for inulin) to 0.3-0.1 (for serum albumin). These patterns have been identified using a variety of indicators, but they have been studied in the most detail using dextrans, which have a wide range of molecular weights (from 10,000 to 2 million). Subsequent studies have shown that the limitation, which increases rapidly with an increase in molecular weight to 70,000, does not change much with a further increase in the size of the molecules up to the giant molecules of b-lipoprotein in the blood plasma (molecular weight of 3 million, effective radius of 40 nm). It is clear that all these regularities could not but suggest the idea of the existence of two types of pores or channels in the wall of microvessels, differing in size and number. Corresponding calculations, based on the size of molecules that are restricted in their passage from the blood to the lymph, have shown that the wall of microvessels can have through cylindrical channels filled with fluid with a diameter of 7–9 nm (small pores), as well as large pores or hatches with a diameter of at least 20 nm. The data indicating the possibility of the existence of two types of pores were obtained in experiments on various organs, the microvessels of which have different types of endothelium: continuous, perforated, intermittent. The difference here was only in the quantitative ratios of large and small pores. For example, in vessels with continuous endothelium, this ratio, according to various authors, lies in the range of 1:10,000-30,000, and in the vessels of the liver (intermittent perforated sinusoid endothelium) it is 1:340. In microvessels with perforated endothelium (intestines, kidneys, etc.), intermediate values are observed. Therefore, the organ gradient of vascular permeability in the light of these data is explained by differences in the ratio of large and small pores. It is believed that the concentration of small pores in vessels with different types of endothelium is approximately the same and is expressed in the value of 10-20 pores/μm2 of the endothelial surface, 0.1-0.2% of which in total is accounted for by small pores, while large pores in continuous endothelium account for only a tiny part of the endothelial surface (about 3-10"[5]). Consequently, in the electron microscopic study of microvessels with continuous endothelium, it is theoretically possible to detect small pores in it, while the probability of encountering large pores here is practically zero. In other types of microvessels, large pores should also be detected by electron microscopic method. Experimental studies have shown that the number of small and large pores is not constant. For example, when venous pressure increases, the number of small pores decreases and the number of large pores increases (Arturson

1972). On the basis of such data, it can be assumed that large pores or hatches function like "relief" or "safety" valves, opening when venous pressure rises to discharge fluid into the interstitium and lymphatic system (Wiederhielm 1968). As for the exact sizes of large and small pores, their calculation is complicated by the lack of necessary data on the geometric, or rather stereometric, characteristics of these supposed structures. The theory of pores admits that they can have a wide variety of shapes (cylinders, slits, etc.), and can also be both continuous (through) and intermittent (diaphragm or "quantized"). The essence of the concept is the idea of the presence in the wall of microvessels of differentiated transport pathways or transport mechanisms that ensure the selectivity of vascular permeability in relation to the size of penetrating molecules. Molecules with a molecular weight of 30,000–40,000 and a radius of about 2-2.5 nm. Molecules weighing more than 90,000 and with a diameter of more than 8 nm are completely excluded. It should be borne in mind that the size of non-spherical molecules is determined in this case by the radius of the sphere that is formed by the rotation of these molecules in the flow (hydrodynamic or effective radius). Therefore, molecules with the same molecular weight may experience different resistance when passing through small pores. This difference is explained by differences in the spatial configuration of the molecules, especially when they pass through non-cylindrical channels. Thus, the starting points for the electron microscopic study of the pathways and mechanisms of transport of substances through the microvascular wall can be: a) data on the presence of an organ gradient of vascular permeability, b) data indicating the existence of a "capillary permeability gradient", and c) the physiological concept of "endothelial pores". Ultrastructural analysis of transport routes and mechanisms[1,6, 11,12,17].

Capillary microvessels with continuous endothelium

Already the first acquaintance with the ultrastructure of this type of microvessels showed that there are no obvious channels or pores filled with fluid. The search for possible equivalents then led to attention to the zones of intercellular contacts and to cytoplasmic structures called micropinocytic vesicles.

The intercellular route of penetration of substances through the endothelium has always been considered the most probable route of transendothelial exchange. Electron microscopic study of the ultrastructure of interendothelial junctions has shown that the contacting surfaces of adjacent endothelial cells form contacts of different density and length. For example, there may be a gap-like gap between the membranes from 4 nm (or less) to 10-15 nm. The width of the same slit fluctuates in the direction from lumen to the basal side, and probably also along the perimeter of the contact area. The most typical are slits with single or

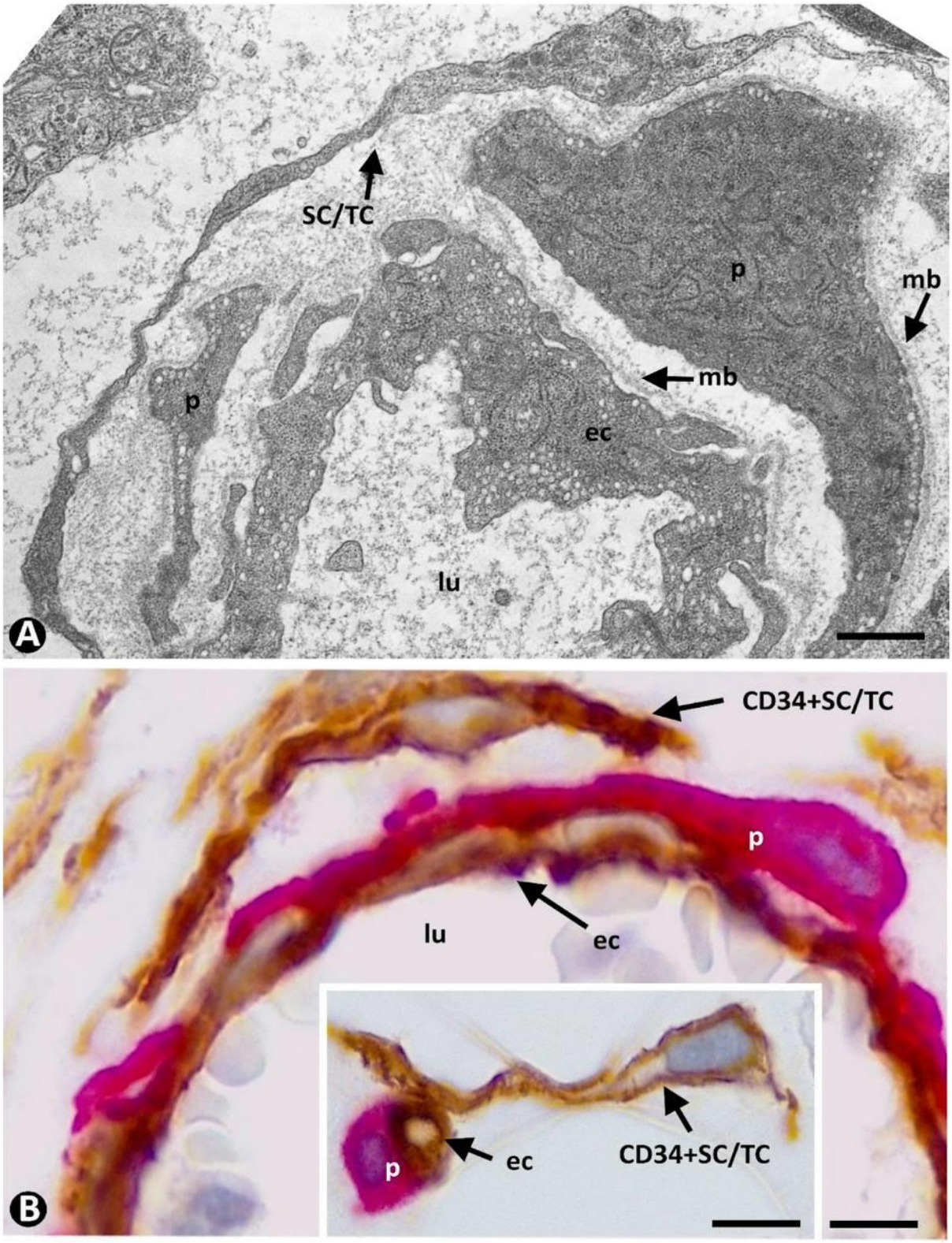
multiple constrictions, in the area of which the articulated surfaces approach by a certain distance, sometimes reaching 4 nm. In the three-dimensional image, such zones of convergence are represented in the form of a belt (continuous or intermittent) that crosses the slit along its entire length and divides it, as it were, into two wider slits (basal and luminal). The width of this girdle is about 20 nm (Karnovsky, 1970). In some cases, the convergence of the articulating surfaces culminates in a partial fusion of the cell membranes. The surface sheets of the three-layered membranes merge, and the fused sheets may remain in place as a continuous dense layer or disappear in the middle part of the contact girdle. In the first case, the confluence zone has a five-layer structure across the width of the entire contact, in the second case, a three-layer structure is revealed in the middle part of the contact: two dense layers and a light layer between them (V. A. Shakhlamov, 1971; Muir, Peters, 1962; Luft, 1965; Bruns, Palade, 1968; Karnovsky, 1968). Thus, electron microscopy has shown that there are indeed slits in the junction area of endothelial cells, in many cases partially or completely blocked by continuous or intermittent (dotted) bands of intercellular contacts proper, which have different densities. It is clear that the contacts accompanied by the fusion of the adjacent cell membranes completely interrupt the structural connection of the lumen of the microvessels with the subendothelial space. However, in most cases, the extent of such contacts is unknown. It is possible that they are only point confluences of the membranes, distributed without any system in the interendothelial cleft and not providing its complete overlap. The intercellular fissures along their entire length from the lumen to the basal surface most often look empty. It is only in the contact areas that some compaction of the substance filling the gap is sometimes detected. However, it is known that the cell wall also contains an "empty" layer in its structure, located between two osmophilic layers, or leaves. Therefore, it is clear that the "electron microscopic void" is only the absence of osmophilicity and the ability to be stained with standard electron microscopic dyes. The use of a new dye, namely ruthenium red, made it possible to reveal a "hairy coating" on the surface of endothelial cells (Luft, 1965). Endothelial cells are covered with this coating on all sides, including the side of the intercellular cleft, so that the intercellular cleft is filled with the substance of the endoplasmic coating along its entire length. In fact, the endoplasmic coatings of adjacent cells meet and merge in the cleft. The thickness of each layer is 15–20 nm along the free cell edge. Therefore, in any type of intercellular contact, the gap must be filled with this polysaccharide substance. It should be noted that the endoplasmic coating on the surface of the endothelium is sometimes revealed by the usual methods of fixation and staining by the same localization as when using ruthenium red (O. V. Alekseev, 1968; V. A. Shakhlamov, 1971; Y. L. Karaganov, 1972). Electron microscopic evidence of the filling of intercellular clefts with a

special substance in a new form has revived the idea of "intercellular cement". The word "cement" is hardly suitable for describing the structure and function of this loose material, which is quite easily permeable to relatively large molecules, as will be discussed below. However, there is no doubt that this substance plays an important role in intercellular permeability, especially in ion transport. Thus, the intercellular clefts, which claim to be the structural equivalent of the "small pores" of physiologists, are in fact ill-suited for this role: in any type of intercellular contacts, they do not appear as continuous channels filled with fluid. For this reason, many researchers, based on the data on the fine structure of the interendothelial clefts, rejected any connection between these structures and small pores (Bruns and Palade, 1968), and sometimes denied the possibility of intercellular transport at all. This issue has been clarified by direct studies of the permeability of the interendothelial clefts. Numerous studies have shown that molecules and microparticles of 5-6 nm in size can hardly penetrate the intercellular spaces and leave the bloodstream. These data were obtained by using plant peroxidase as electron microscopic indicators (Karnovsky, 1967, 1968, 1970; Schneeberger-Keeley, Karnovsky, 1968; Feder, E. A., 1969; Olsson, 1971, et al.), iron oxide saccharate (Florey, 1964), hemoglobin (Pietra, 1969), myoglobin (Anderson, 1972), surfactant of the alveolar lining (Dernier, 1969), colloidal iron (V. A. Shakhlamov, 1971). Smaller molecules penetrate through the slits much more easily: cytochrome C (Karnovsky and Rice, 1969), microperoxidase (Feder, 1971), and crystalloids (Ohori, 1963; Casley-Smith, 1969; Brauser O. A., 1971). At the same time, important differences were revealed in the group of capillaries with continuous endothelium, namely, lower permeability of interendothelial clefts in the capillaries of the brain (Reese and Karnovsky, 1967; Feder, E. A., 1969; Brightmann E. A., 1970), retinas (Shtakib, Cunha-Vaz, 1966; Hoves, E. A., 1970; Shabo and Maxwell, 1972), peripheral nerves (Olsson, 1971), i.e., in those organs and tissues where there are specialized histo-hematic barriers. Comparing this fact with the results of the study of the ultrastructure of the slits in the microvessels of these areas, it can be concluded that here the slits are covered by belts of intercellular contacts along their entire length, while in other organs (in the heart, muscles, lungs, etc.) endothelial cells do not have a continuous tight contact, which provides a higher permeability of the slits. From the above materials, it can be seen that there may be subtypes among the main types of blood capillaries. In this case, we have two groups of capillaries with continuous endothelium, but significantly different in its barrier properties. It is clear that in terms of their functional properties, the interendothelial clefts correspond to the "small pores" of physiologists. Quantitative discrepancies (Bruns and Palade, 1968; Karnovsky, 1970) are most likely due to the errors of both methods (physiological and electron microscopic) (Karnovsky, 1970). The functional role

of polysaccharides filling interendothelial clefts remains unclear. It can be assumed that they ensure the cleavage of molecules and ions from plasma proteins, with which they bind when they enter the blood. It is known, for example, that plant peroxidase (the most common electrotronic microscopic indicator), when it enters the blood, binds to globulins, and relatively strongly, since during electrophoretic acceleration it moves along with globulins. Obviously, in combination with globulin, peroxidase cannot penetrate into the gap (due to the large size of the globulin). Therefore, before entering the cleft, this complex must disintegrate, and it does disintegrate—the peroxidase in most capillaries exits the blood through the gaps between the endothelial cells. Based on the general properties of polysaccharides, it is logical to assume that it is with their participation that the destruction of such complexes occurs. There is no experimental evidence to support (or against) this assumption.

Microvesicular transport. Its discovery and experimental study is one of the most important achievements of electron microscopy in research on transcapillary exchange. The discovery of vesicular elements in the cytoplasm of endothelial cells, the elucidation of the mechanisms of their formation from the surface membrane, and the proof of their participation in the transendothelial transfer of substances — all this is associated with the name of the outstanding American researcher Palade. In 1953, he was the first in the world to describe the ultrastructure of blood capillaries. It can be said that the history of the study of microvesicular transport begins with this work. In the cytoplasm of endothelial cells, J. Palade discovered spherical elements bounded by an elemental membrane and filled with light contents. They could be compared to air bubbles suspended in the cytoplasm. A large number of these vesicles were associated with the superficial membrane by a narrow neck. These are fixed flask-shaped bubbles. It was concluded that free cytoplasmic vesicles are formed from fixed flasks, which in turn are formed by local retraction of the surface membrane. There was a resemblance of this process to what was previously known from light microscopy, namely pinocytosis, which had been discovered 30 years earlier by Lewis. For this similarity, the process of microvesicle formation was called "micropinocytosis", which emphasized the morphological difference and functional similarity of both processes, which culminate in the absorption of extracellular fluid. Therefore,

microvesicles are often referred to as micropinocytic vesicles. Noting that microvesicles, after formation, are freely distributed throughout the cytoplasm and can reach the opposite cell surface, J. S. Smith. Palade suggested the possibility of transendothelial transport of substances by means of these structures. It was assumed that, having formed on one surface, the microvesicles cross the cytoplasm, reach the opposite surface, where they connect with the cell wall and are freed from the fluid captured in the process of formation. This assumption was met with skepticism, especially since subsequent electron microscopic studies revealed a universal prevalence of microvesicular elements: they were found in almost all cell types and in all animal species studied. Such a wide prevalence of micropinocytosis makes it one of the fundamental biological processes, the importance and role of which have not yet been precisely determined, as well as the underlying mechanisms underlying it. Indeed, what are the causes of indentation of this or that area of the cell surface? What regulates the size of this indentation, which culminates in the formation of standard-sized vesicular structures? How can we explain the fact that in some cases (much less frequently) the retraction of the cell surface is more extensive and not a standard microvesicle is formed, but a more voluminous vesicular structure, a vacuole? Why doesn't the "timely" unlacing of microvesicles sometimes occur? What causes the formation of deep blind channels that almost reach the opposite surface of the cell? By now, quite a few such questions have accumulated, and almost all of them still remain unanswered. What is clear is that micro-vesiculation is a special property of superficial cytoplasmic membranes, reflecting either the peculiarity of their chemical structure or the peculiarity of their position: at the boundary between the external environment and the cytoplasm. In general, the formation of microvesicles is one of the main manifestations of the vital activity of surface membranes, including the plasmolemma of endothelial cells. Microvesicles are distributed unevenly throughout the cytoplasm of endothelial cells. They are found in greater numbers in the peripheral regions than in the area of the nucleus. These elements are formed on the luminal and basal surfaces of endothelial cells, as well as in the area of intercellular junctions, although much less frequently. Vesicles lying freely in the cytoplasm are most often presented as isolated elements, but sometimes they join together to form connected chains or complex figures (Figure 4).



(**A**): Ultrastructural image of a small vessel of the pericytic microvasculature with endothelial cells (ec) in the intima, pericytes (p) in the media, and processes of stromal cells/TCs (SC/TC) in the adventitia. Note a basal membrane (mb) shared by endothelial cells and pericytes. (**B**) and insert: Endothelial cells (ec, brown) in the intimal layer, pericytes (p, red) in the media layer, and CD34+SCs/TCs (brown) in the adventitia in a venule (**B**) and a capillary (insert of (**B**)) in a very initial stage of angiogenesis during granulation tissue formation. Vessel lumen: lu. (**A**): Ultrathin section. Uranyl acetate and lead citrate. (**B**) and insert: Double immunochemistry for CD34 (brown) and αSMA (red). Bar: (**A**): 0.8 µm; (**B**): 8 µm.

The average diameter of free microvesicles is 70–75 nm. This value is influenced by the method of fixation (Bruns and Palade, 1968). There is no division of microcytic vesicles by size into any populations (Bruns and Palade, 1968; Casley-Smith, Clark, 1972). The volume of a microvesicle is on average 0.00017 μm3. About 50% of this volume is occupied by the bounding membrane, so that the capacity of the microvesicle with an inner diameter of 55 nm is 0.000083 μm3. In the process of formation, the vesicle is connected to the superficial membrane (all its layers pass into the vesicle shell) by a narrow neck that is up to 20 nm long, has an outer diameter of about 30 nm, and an inner diameter of about 15 nm. Such a neck is formed only immediately before the microvesicle is laced into the cytoplasm, and only at this stage can it prevent particles larger than 15 nm from entering the microvesicle. The microvesicle is "loaded" directly in the process of its formation. Microvesicles can also be connected to the surface without the help of a neck or neck. In this case, the cell membrane passes directly into the membrane of the vesicle itself. This method of communication is interpreted as a pattern of fusion of a microvesicle with a plasmolemma. The cone-shaped form of the bond is considered as an ultrastructural expression of the process of microvesicle formation from the membrane (Palade and Bruns, 1968). The possibility of such a distinction between vesicles that form and merge with the surface has not yet been widely studied, but it is of great interest. The number of bound and free microvesicles (their sum) varies with endothelial thickness ranging from 400 to 2000 vesicles/μm3 of the cytoplasm with a change in thickness from 0.4 to 0.1 μm, respectively (Bruns and Palade, 1968). This is understandable if we take into account that the formation and disappearance of microvesicles are mainly related to the activity of the cell surface and to a much lesser extent to their fate in the cytoplasm, which in this case acts as a variable capacity. It is clear that with a change in the thickness of the cytoplasm in an inverse ratio, the amount of cell surface area per unit volume of the cytoplasm changes; Accordingly, the number of microvesicles per unit volume should also change. Our calculations show that normally, any volume of cytoplasm bounded on the basal and luminal sides by membranes with an area of 1 μm2 contains an average of about 220 vesicles, i.e., there is a relatively constant number of microvesicles per 1 μm2 of the luminal (and, accordingly, basal) surface of blood microvessels (with an endothelial thickness of 0.2-0.4 μm). Casley-Smith (1969) also drew attention to the existence of such a pattern, studying the vesicular system in the endothelium of blood and lymphatic capillaries, the aorta, as well as in the cells of the mesothelium, which is similar in its permeability to the vascular endothelium. According to his data, the indicator of the number of bound microvesicles per 1 μm2 of the surface is particularly constant. This indicator is the same for the endothelium of the blood and lymphatic capillaries and for the mesothelium. In this regard, it should be noted

that the separation of microvesicles into free and morphologically bound by morphological criteria in ultrathin sections gives a large percentage of error due to the "failure to get into the cut" of the sections of the vesicle connection with the membrane. Such a distinction is feasible only by studying serial sections, constructing spatial models of endothelial regions, as was done by Bruns and Palade (1968), and using electron microscopic labels (Karnovsky, 1968; Karnovsky, Shea, 1970). In the latter case, lanthanum hydroxide is used, which fills the intercellular spaces and those cytoplasmic structures that have a direct connection with the extracellular environment in pre-fixed tissues. Using this indication, it was found that most of the microvesicles, which are located at different distances from the cell surface and have no visible connection with it, are stained with an indicator. However, this method is also not flawless, since it is possible to stain vesicles not because of their direct connection with the surface, but through intermediate vesicles by the mechanism of chain-vesicular transport (along a chain of vesicles opening into each other, the outermost of which is connected to the surface). Therefore, we believe that the most convincing data on the ratio of bound and free vesicles can only be obtained by using serial sections with or without building a three-dimensional model. This task is facilitated by the fact that the size of the microvesicles fits into 2-3 ultra-thin sections. For example, the model built by Bruns and Palade is based on only 7 serial cuts. From this model, it is clear that 43% of the total number of vesicles are associated with the basal surface, 28% with the luminal surface, and 29% are freely located in the cytoplasm (in a 0.3 μm thick section of the endothelium). These figures are close to the corresponding values obtained by V. A. Shakhlamov (1971) for the endothelium of venous capillaries: 49% are associated with the basal surface, 20% with the lumial surface, and 31% are freely located in the cytoplasm. For the endothelium of arterial capillaries, he obtained slightly different figures: 32% are associated with the basal surface, 20% with the luminal surface, and 48% are free. From these data, it follows that in arterial and venous capillaries, the percentage of vesicles associated with the lumial surface of the endothelium is the same, while the ratio between free and basal vesicles is reversed during the transition from the arterial to the venous region: first free vesicles predominate, and then those associated with the basal surface. It seems that the connection of microvesicles with the membrane is facilitated in the venous region (the transition of free vesicles into bound vesicles is accelerated), although another explanation cannot be ruled out, namely, that the separation of vesicles formed on the basal surface is difficult here (the transition of bound vesicles to free vesicles is slowed down). If the connection of free vesicles with the basal surface is really accelerated in the venous region, then this may be one of the basis of the phenomenon of "capillary permeability gradient", i.e., a more significant transfer of macromolecules in the

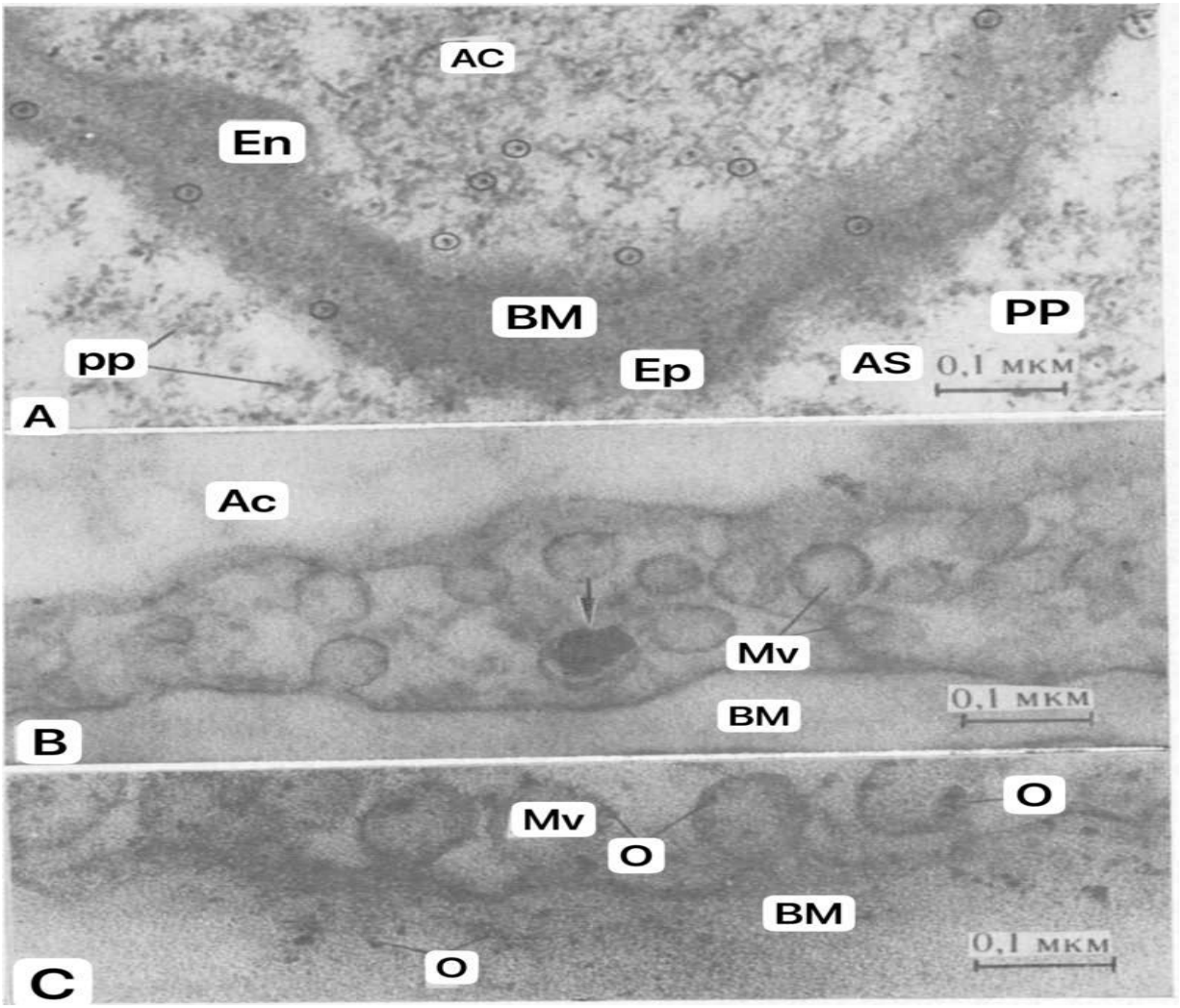
venous region of microvessels. It is clear that further comparative studies of the microvesicular system in the endothelium of different parts of the microvasculature network are needed. In recent years, the question of the stability of the microvesicular system in endothelial cells has been relatively widely studied. It has been shown that prolonged compression of venous or arterial vessels (up to 40 min), tissue cooling, the use of glycolysis inhibitors, changes in perfusion pressure, etc., do not have any significant effect on the number and size of microvesicles in the endothelium (Casley-Smith, 1965, 1969; Jennings, Florey, 1967; Marquart, Caesar, 1970, et al.). Only with the development of pronounced cellular edema (40-minute shutdown of blood flow) is there a decrease in the concentration of microvesicles in the vascular endothelium, which is explained by the dilution effect, and not by a decrease in their absolute number. Such stability of the microvesicular apparatus is interpreted by some researchers, firstly, as evidence of the non-involvement of these structures in transendothelial transport of substances (Marquart, Caesar, 1970), and secondly, as an indication of the complete independence of the microvesicular process from energy processes in the cell (Casley-Smith, 1965, 1969). It is hardly possible to agree with both interpretations of this fact, especially with the first. It is clear that exposures that do not lead to rapid changes or damage to biological membranes will not affect the preservation of microvesicles or their number. At the same time, factors that change the state of biological membranes in general should also affect microvesiculation. Indeed, general X-ray irradiation of animals, which is well known to have a similar effect on membranes, leads in the initial period to an increase in vesiculation in the endothelium and, in addition, to the appearance of microvesicles and vacuoles in erythrocytes (O. V. Alekseev, 1968; O. V. Alekseev, A. M. Chernukh, 1969; Chernukh, Alexeyov, 1969). This effect was observed in the first hours after irradiation and only in those endothelial cells that did not yet show signs of destruction of surface membranes. Interestingly, erythrocytes with microvesicles are often found in the blood of newborns, but very rarely in adults (Blanton e.a., 1968). The endothelium in newborns also has an increased number of microvesicles, which is associated with the presence of high metabolism in this age period. In order to solve the problem of the energy dependence of the micropinocytic process, it is first necessary to take into account the fact of the presence of active ATPase in microvesicles (V. A. Shakhlamov, 1971; Marches!, 1963, 1964; Torack, Barrnett, 1964; Hoff, Graf. 1966; Campbell, 1968; Sukekuni, 1972). ATPase appears to be present in all parts of the cell membrane, but it is found in its active form only in microvesicles and at the sites of their formation, where there are only shallow indentations of the cell surface. The causes of local activation of ATPase are unclear. The fact that when the lungs or heart are perfused with blood containing adenine nucleotides, their breakdown products immediately appear in the outflowing

blood indicates that the ATPase of the microvesicles is actively working and therefore energy is released (Smith and Ryan 1970). It is not known what this energy is spent on, but it is very possible that only the processes of interaction of vesicles with the cell membrane are epergic-dependent, and not their movement in the cytoplasm after lacing (Karnovsky and Shea, 1970). On the other hand, it is known that ATPase activity in microvesicles is not detected in all capillaries. For example, it is absent in the microvesicles of the capillaries of some parts of the brain (Marchesi and Barrnett, 1964; Joo, 1969). This suggests that there is no absolute dependence of microvesiculation on ATPase activity. The question of the degree of dependence of micropinocytosis on the energy of macroergs remains open. Of particular interest are the data obtained in the study of pinocytosis in amoebas (Brandt and Freeman, 1967). Substances that enhance pinocytosis cause a 50-fold decrease in the electrical resistance of membranes and increase the permeability of the membrane before the formation of typical intussusceptions and vacuoles. The thickening of the membrane is determined electronically microscopically, mainly due to the expansion of the middle leaflet (light). The addition of calcium ions inhibits these changes, the addition of NaCl causes them. It is possible that during the formation of microvesicles in endothelial cells, some similar changes occur at the membrane level. The issue needs to be specially studied. Before proceeding to consider the role of microvesicles in transendothelial transport of substances, let us summarize some conclusions based on the data presented above. In summary, micropinocytosis (or cytopemsis) can be considered as a fundamental cellular process most developed in endothelial cells, where microvesicles are typical and stable cytoplasmic organelles. Unlike other cytoplasmic organelles, they are genetically and functionally related to the cell membrane and reflect its biology and functional state. Micropinocytosis occurs on the entire surface of endothelial cells, both on the side of the bloodstream and on the basement membrane side. Microvesicles have high metabolic activity (they contain ATP-ase, as well as alkaline phosphatase, cholinesterase and, according to some data, aspartate-aminotransferase), which justifiably allows us to refer them to the category of dynamic, but constant subcellular organelles, the activity of which is aimed at meeting cellular needs and is accompanied by a regulatory effect in relation to the composition of the immediate environment, primarily the composition of blood. This regulatory effect is due to both metabolic and absorption (micropinocytic) activity of the microvesicular system. With the help of microvesicles, macromolecules of any size, contained or appearing in the blood plasma, as well as in the subendothelial space, can enter endothelial cells. The study of micropinocytosis in various types of cells has led to the conclusion that, in general biological terms, it is only one of the mechanisms of endocytosis, i.e., the absorption of solutions and microparticles by cells,

carried out due to the activity of the cell surface, with the help of various derivatives of this surface: short and long folds; canal-shaped, slit-like, superficial and deep depressions, etc. (O. V. Alekseev, 1968; Y. L. Karaganov, 1972; Novikov, 1963; Fawcett, 1965). Estimating the functional significance of endocytic processes in the endothelium, B. Zweifach (1962) came to the conclusion that phagocytosis, macro- and micropinocytosis perform one function in the animal organism: purification of the blood flow from solid particles (phagocytosis) and from altered plasma proteins (micropinocytosis). Hence, micropinocytosis is phagocytosis at the molecular level, the peculiarity of which is that altered macromolecules are phagocytosed, and under abnormal conditions, microparticles are also phagocytosed. It should be noted that there is currently no data confirming the "targeting" of micropinocytosis on altered proteins. Taking this into account, we refrain from such a characterization of micropinocytosis, but we fully support the main idea, namely, the protective and regulatory function of endocytic mechanisms in the endothelium in terms of maintaining the constancy of the composition of blood and interstitial environment in normal and especially pathological conditions (O. V. Alekseev, 1968; O. V. Alekseev, A. M. Chernukh, 1969; Cher-nukh, Alexeyev, 1969). The versatility of micropinocytosis and the polyfunctionality of micropinocytic vesicles with a predominance of the absorption function at first glance exclude the possibility of transendothelial transfer of substances with the help of these organelles. At one time, these arguments were put forward to refute the hypothesis of the transport function of microvesicles (Florey, 1964, et al.). In our opinion, it is in the polyfunctionality of microvesicles with a predominance of the absorption function that we should look for the origins of their transport function. The emergence and formation of this function were ensured by the peculiarity of the position of endothelial cells (at the boundary of two media) and the corresponding feature of the endothelial function: the delimitation and binding of two media, interstitial and blood. Evidence of the transport function of microvesicles was obtained by electron microscopic study of the exit pathways of macromolecules and microparticles from the bloodstream. These experiments have shown that within a few minutes after intravenous administration, microparticles of thoro-trust, mercury sulfide, colloidal metals, iron oxide saccharate, ferritin molecules, molecular indicators with peroxidase activity, dextran molecules, etc., can be detected in microvesicles (Majno and Palade, 1961; Palade, 1961; Pappas, Tennyson, 1962; Jennings e. a., 1962; Palade, Bruns, 1964; Florey, 1964, 1966; Casley-Smith, 1964, 1965; Jennings, Florey, 1967; Karnovsky, 1967, 1968, 1970, etc.). In these studies, it was possible to identify not only the fact of the entry of tracers into microvesicles, but also to trace all stages of the transport process: the loading of microvesicles in the process of formation on one cell surface, the transfer of tracers in vesicles to the opposite

surface, the release of tracers into the subendothelial space. Important results have been obtained in experiments studying ferritin transport by microvesicles (Shirahama and Cohen, 1972). In this work, rabbits were injected with a ferritin solution intravenously and after a while pieces of the myocardium were taken for electron microscopic study. In the process of preparation, the preparations were stained with ruthenium red, revealing the endocapillary layer. This layer, up to 0.1 μm thick, was found on the surface of endothelial cells and as a narrower rim within the microvesicles that is connected to the membrane. It was found that the transported ferritin molecules were located inside the mucopolysaccharide coating lining the vesicles from the inside, rather than in the center of the microvesicle. These data illustrate the important role of the endocapillary layer in the transport of macromolecules and allow us to reasonably assume that the adsorption of macromolecules on the endothelial surface is the first link in the mechanism of vesicular transport. It is clear that at this stage the separation of molecules into "permissible" and "non-skippable" can be carried out, i.e., the selectivity of transport can be ensured: selective adsorption as the basis of selective transport. It can also be assumed that it is the interaction of adsorbed molecules with the epdocapillary layer at the site of adsorption that locally changes the state of the cell membrane and triggers the mechanism of microvesicle formation in this region, which leads to the absorption of adsorbed macromolecules. In this way, self-regulation of micropinocytosis and transendothelial transport can take place: the more molecules are adsorbed, the more microvesicles are formed. In this regard, it would be interesting to compare the ability of plasma proteins with our "electron microscopic indicators" to induce pinocytosis, for example, in amoeba. It is possible that the poor development of microvesicles by most indicators is explained not only by their relatively low concentration in the blood (up to 1-3%), but also by their poor adsorption capacity. It is known, for example, that the absorption of ferritin in the presence of gamma globulin is much lower than that of ferritin conjugated with it (Aston et al., 1962). The size of such a complex is 2 times larger than the size of one ferritin. Peroxidase, which is good at detecting polysaccharide cell coatings, has also been shown to mark or work microvesicles in endothelial cells. All these facts suggest that microvesicular transport is closely related to the adsorption of substances on the endothelial surface and that the selectivity of transport is due to the adsorption properties of the cell surface. It is clear that substances that are poorly adsorbed on the endothelial surface cannot be good indicators of microvesicular transport. In the conditions of pathology accompanied by changes in the state of the endothelial surface, it is possible to increase its adsorption capacity and more successfully use "bad indicators" to identify the transport capacity of micropinocytic vesicles. Such a shift has been observed in experimental vagus neuritis. In this case, microvesicles labeled with iron oxide

sacrate were much more common in the endothelium of the microvessels of the lungs and heart, and even microvesicles labeled with colloidal charcoal (ink particles) were detected, which was never observed normally (Fig. 5). A similar shift was observed in the experimental sludge syndrome. Both types of pathology are accompanied by changes in the adhesive properties of the endothelial surface and blood cells, which could be judged by the adhesion of blood cells to the endothelium and the phenomena of intravascular aggregation. In the light of all these data, the question of the relationship between microvesicular transport and the phenomenon of surface adsorption seems to us to be very important. It is in pathology, when atypical or altered macromolecules appear in the blood, that micropinocytosis and microvesicular transport must appear in all their functional force, which would be impossible without a corresponding change in the state of the plasmolemma and its polysaccharide coating. These changes are taking place, but a more or less in-depth characterization of them has not yet been obtained, which may be the task of further research. Recently, much attention has been paid to the study of the velocity (linear and volumetric) of microvesicular transport. According to various sources, the rate of transfer, or life cycle [1,6, 11,12,17].



Picture.5. Diffuse transfer (A) of ferric oxide saccharate microparticles from the lumen of the alveolar capillary (Ap) to the alveolar space (As) together with plasma proteins (pp) in experimental sludge siidrome in rats.

Individual dense particles of 3–5 nm (o) in size are visible in the thinned endothelium (En), basement membrane (BM), and alveolar epithelium (EP), as well as in the lumen of the capillary and alveolus, B — microvesicular transport of colloidal carbon particles (arrow) in the capillary of the rabbit myocardium in vagus neuritis (impaired selectivity of vesicular transport), C — increased microvesicular transfer of iron oxide (O) saccharate in vagus neuritis. Saccharate particles are seen in microvesicles (MV) and in the basement membrane (BM', a — fixation in a mixture of 2% paraformaldehyde and 2% glutaraldehyde without subsequent osmium fixation of the contrast of the sections; b and c — osmium fixation without contrasting microvesicle sections, currently estimated at 1–9 s, with the bulk of this time occurring at the stages of formation and connection of microvesicles with the surface membrane (Casley-Smith, 1969; Tomlin, 1969; Shea, Karnovsky, Bossert, 1969; Karnovsky, Shea, 1970; Green, Casley-Smith, 1972). The results of calculating the volumetric velocity of microvesicular transport are more homogeneous: 6–10 vesicles/μm2 of the endothelial surface for each second and in each direction (Karnovsky and Shea, 1970; Renkin, 1970; Casley-Smith, Clark, 1972). These data were obtained by calculation based on the results of quantitative ultrastructural studies of the microvesicular system in the endothelium. We tried to determine the speed of vesicular transport in a direct way. The experiments were carried out on an isolated rabbit aorta dissected longitudinally. Plasma containing 1% ferritin or 1% iron oxide saccharate was applied to the endothelial surface. After 5-10-20 seconds, the pieces of the aorta taken for the experiment were frozen with the help of a massive copper rod cooled in liquid nitrogen. For better preservation of the endothelial structure, the rod was applied to the aorta from the side of the adventitia. The frozen piece was immediately placed in a cooled fixative and preparations for electron microscopic examination were prepared in the usual way. Single labeled vesicles in the endothelium were detected after 5 s, and they were detected in the basement membrane for the same period. Thus, direct studies have shown that the life cycle of microvesicles (from loading to unloading on the opposite side) is greater than 5 s. To assess the physiological role of microvesicular transport, simple calculations were made. A section of the capillary with an internal diameter of 5 μm and a length of 1 μm was taken. The capacity of this region is 19.6 μm3, and the endothelial surface area is 15.7 μm2. Taking into account the data that 14 microvesicles depart from 1 μm2 of the endothelial surface per second, 7 of which reach the opposite surface, it is determined that about 110 "transport" microvesicles with a total capacity

of 0.0093 μm3 are launched from a surface of 15.7 μm2 per second, i.e., 0.0093 μl of plasma is transported by microvesicles every second. Therefore, 19.6 μm3: 0.0093 μm3 = 2108 (s). Thus, in 35 minutes, the endothelium of the capillary bed can transport a volume of plasma equal to the capacity of the capillary bed into the pericapillary space with the help of vesicular transport. Taking into account the correction for hematocrit, this time is almost halved (to 18 minutes). At the same rate, the endothelium transports the macromolecular solution from the pericapillary space into the bloodstream. Moreover, if we take into account that only about 50% of the total number of start-up vesicles participate in transport (Casley-Smith and Clark, 1972), we must conclude that in less than 9 minutes the endothelium will contain all the plasma that simultaneously fills the capillary bed. Figuratively speaking, if the blood flow is stopped and all types of transcapillary exchange are blocked, leaving only microvesicular transport in the direction from the blood to the tissue, then in 9 minutes all the plasma will disappear from the lumen of the capillary bed, half of it will be in the pericapillary space, and the other half will be deposited in the endothelium itself. These figures clearly show the important role of micropinocytosis, microvesicular transport, in maintaining the constancy of blood composition. It should be noted that the calculations presented are very approximate due to the fact that the initial data are constantly being revised. For example, instead of a value of 7 vesicles/μm2 per second, it would be possible to take 10 or 13 vesicles/μm2 per second, which would give results l'/y-2 times different (lower) from those presented. It is possible that in different organs where capillaries have a continuous endothelium, the volumetric velocity of microvesicular transport is not the same. Future research should answer this question as well. As mentioned earlier, physiologists, analyzing the dynamics of the exchange of macromolecules through the wall of microvessels, created a concept called pore theory. According to this theory, there must be channels in the continuous endothelium that allow macromolecules such as ferritin to pass through the endothelium. Electron microscopy has shown that such molecules are transported in the continuous endothelium not through channels, which, according to physiologists' calculations, are practically impossible to find using an electron microscope, but are transported by microvesicles, which are easily detected by this method of examination. Functionally, microvesicular transport is fully consistent with physiologists' ideas about large pores in the endothelium. The structural characteristics of these pores are not consistent with the morphology of vesicular transport. But, as physiologists themselves believe, the essence is not in the form, but in the content. Therefore, it is now generally accepted that microvesicular transport is the equivalent of the idea of large-pore transport. In addition, there is the idea that microvesicles can also act as equivalents of small pores (Bruns and Palade, 1968), allowing rapid penetration of

micromolecules through the endothelium. Such equivalents, according to Bruns and Palade (1968), appear when microvesicles are arranged in a chain from one surface to another, partially fusing with each other (Fig. 60), resulting in the formation of a transendothelial canal. The capacity of such a channel is determined by the size of the mouths in the places of partial fusion of micro vesicles by the tips. This assumption has hardly been investigated. However, in some illustrations (e.g., Figure 13 by Karnovsky, 1968) it is possible to see chains of microvesicles extending deep into the cytoplasm, filled with laptap hydroxide. In these studies, lanthanum was added to the fixator to work out the interstitial spaces and micropores, as well as to identify the connections of microvesicles with the external environment (with the lumen of the vessel or with the subendothelial space). It is unlikely that the vesicles that make up such a chain are separately associated with the cell surface. Most likely, they open into each other, and the outermost vesicle is connected to the surface, which allowed lanthanum to fill the entire chain. In pathological conditions, such chains can form through channels with high throughput — micropores. All these data suggest that microvesicles can also act as equivalents of small pores that transmit molecules no larger than 7-8 nm. The issue needs to be further studied. In conclusion, it can be said that the discovery of micropinocytosis in the endothelium naturally led to the discovery of microvesicular transport. Microvesicles, while performing a transport function, are at the same time multifunctional organelles containing a number of enzymes, including ATP-ase, which indicates their important metabolic activity. The microvesicular apparatus of endothelial cells must play an essential role in the protection and regulation of the interstitial environment and especially the blood. Micropinocytosis and microvesicular transport are directly related to the function of the cell wall and its mucopolysaccharide coating. The selective binding of macromolecules to this coating (selective adsorption) is one of the bases of the selectivity of microvesicular transport. Many questions related to the underlying mechanisms of micropinocytosis and microvesicular transport and the elucidation of the role of these processes in various conditions of normal and especially pathological conditions require further study and close attention.

PERMEABILITY OF POROUS ENDOTHELIUM

Microvessels with perforated endothelium are typical for organs in which, due to functional features, there is a transcapillary transition of large amounts of macromolecular substances and fluid. This includes primarily the kidneys, then the intestines, endocrine and exocrine glands, choroid plexus, ciliary processes, and synovial membranes. Less typical are perforated microvessels in loose connective tissue (Maynard E. A., 1957), in the skin (Seifert, Klingmuller,

1972; Takada & Hattory, 1972), in fascia (Rhodin, 1968), in plantar pads (Casley-Smith, 1967). In addition, perforated capillaries (vasa vasorum) are found in the wall of the aorta of humans and rabbits and are not found in the aorta of monkeys, dogs, and rats (Shimamoto e. a., 1968). These species differences are thought to play a role in atherogenesis in humans and rabbits. Recall that physiological studies have revealed a higher permeability of vessels in organs with fenestrated capillaries. According to pore theory, this is due to an increased number of large pores. Electron microscopic examination of perforated microvessels has easily revealed (in contrast to microvessels with continuous endothelium) ultrastructural equivalents of the large pores of physiologists. These equivalents turned out to be indeed pores permeable to ferritin, large-molecule dextran, and even particles of colloidal carbon (ink) (Palade, 1961; Farquhar, E. A., 1961; Florey, 1968; Karnovsky, 1968; Shimamoto E. A., 1968; Clementi, Palade, 1969; Casley-Smith, 1970; Simionescu e. a., 1972). The question of the permeability of fenestra (pores closed by diaphragms) remains unclear. According to some data, the diaphragms of fenestra transmit only micromolecular substances and act as equivalents of small pores of physiologists (as well as intercellular junctions) (Pappas and Tennison, 1962; Florey, 1964; Brigh-mann, 1967; Karnovsky, 1968; Mauli, 1969). According to other authors, diaphragms allow glycogen and dextran particles to pass through (Simionescu E. A., 1972). Most likely, these differences are due to the heterogeneity of the diaphragms that overlap the pores: in one case, the diaphragms are formed by reduced layers of the cell wall, in the other only by a polysaccharide coating capable of imitating the diaphragm (Luft, 1965). Be that as it may, we have to admit that fenestra in the microvessels of different organs have different permeability. This seems to be the reason for the differences in the permeability of fenestrated microvessels in various organs, for example, in the intestines and kidneys (Clementi and Palade, 1969; Simionescu, E. A., 1972). The application of the "freeze-etching" method made it possible to identify the fine structure of the diaphragms and determine how they act as equivalents of small pores. According to Maul (1969), the endothelium has 64 nm octagocal fenestra in rat kidney capillaries. The diaphragm is arranged like a sieve: it contains 3 or 4 concentric fibrous rings, overlapped by radial fibers of 1.5-2.5 nm in size. The gaps are closed by a network of the same fibers. The small size of the cells does not allow large molecules such as ferritin (diameter 11 nm) to pass through the diaphragm, but does not exclude the penetration of smaller molecules, such as plant peroxidase. In contrast to microvessels with continuous endothelium, microvesicular transport of macromolecules and intercellular penetration of micromolecules play a significant role only in those fenestrated vessels where there are poorly permeable fenestra or the total number of pores is insignificant. In most of these vessels, the main flow of substances goes through the pores and

phenesters. It should be emphasized that, despite the absence of formed diaphragms in the area of open pores, there is still some limitation in the rate of penetration of macromolecules. This limitation is probably due to the presence of a substance similar to the material of the endocapillary layer, so that direct contact of the plasma with the basement membrane in the area of open pores is excluded. The basement membrane in capillaries with perforated endothelium, as elsewhere, plays the role of a "coarse" filter, trapping particles larger than 11 nm. Molecules and particles larger than this size do leak through the basement membrane, but this process is very slow and it is possible that this seepage is in some cases due to a local disruption of the basement membrane by the action of extensive accumulations of foreign particles used as an indicator [12,17].

Permeability of the wall of sinuses and sinusoids

Physiological studies have shown that the walls of the sinuses and sinusoids have the greatest permeability. The ratio of large to small pores here is 1:340. At the same time, numerous electron microscopic studies of the fine structure of the wall of these microvessels led to the conclusion that the wall of sinusoids cannot function as a barrier with the property of selective permeability. The basis for this conclusion was the discovery of wide intercellular slits in sinusoids, more precisely, hatches with a diameter of up to 10 μm. In recent years, it has been shown that there are not only intercellular hatches, but also transendothelial pores that are wider than in a typical perforated endothelium (Wisse, 1970, 1972; Song, Groom, 1972). Indications of the presence of pores in sinuses and sinusoids have been encountered before, but conclusive evidence has been obtained only in recent studies. It is clear that in the presence of such openings in the endothelial lining and the absence of a basement membrane, which is characteristic of sinusoids, their wall cannot exclude the penetration of any molecules into the perisipusoid space. In other words, the blood-parenchymal barrier cannot exist in the liver, spleen and bone marrow, since the blood plasma is in direct contact with the parenchyma. The role of endothelial and reticuloendothelial cells here is limited to limiting the area of free contact between plasma and parenchyma. In this case, the specificity of the distribution of substances between the blood and the parenchyma should be determined by the peculiarities of tissue permeability and the sorption capacity of the organ. However, the data available in the literature and the results of the research of these authors allow us to doubt the indisputability of such ideas. For example, it is known that the concentration of protein in the lymph flowing from the liver is close to, but not equal to, its concentration in blood plasma. This indicates that there are restrictions on the penetration of macromolecules from the blood into the lymph, and this restriction must be manifested either at the level of the sinusoidal wall or in the Disse space. However, the structural basis for such an

action of the wall or Disse space seems to be absent: hatches in the endothelium, blood plasma in the Disse space. Studies of the size of the perisinusoidal space using molecules of different sizes have shown that as the molecular weight of substances increases, the capacity of the perisine space progressively decreases (Goresky, 1970). This fact can only be explained by the fact that the Disse space is not filled with plasma, as is believed, but with a high-molecular-weight structured polymer exhibiting the "excluded volume effect" known in polymer chemistry. On the other hand, the success of detecting two types of pores in sinusoids (Mayerson E. A., 1960; Arturson, 1972) points to the possibility of a "filtering" effect at the level of the endothelial lining itself. The above physiological facts, as well as the fact that reticular fibers of protein-polysaccharide nature are located in the Disse space, and Kupffer cells participate in their formation (Friederici and Pirani, 1964), all this allows us to assume the presence of the main intercellular substance in the intercellular spaces and in the Disse space, and not blood plasma. The Disse space, in this case, is the equivalent of the basement membrane. Electropnomicroscopic detection of the base substance is difficult, as well as polysaccharide coatings of various cells. The "voids" revealed by this method in the interstitium illustrate this point well. A. Policard and A. Collet (J966), on the basis of the fact that the Disse space, although weakly stained, is still stained by the PAS reagent, believe that it contains mucopolysaccharides of the same type as the basic substance of connective tissue. Believing that the Disse space is equivalent to the basement membrane, the same authors point to the existence of atypical basement membranes in the microvessels of some endocrine glands, where "a special condensation of glycoprotein material is found, giving the impression of a basement membrane." In this regard, it should be noted that in the sinusoids of the liver, basement membranes, which are well detected by the electron microscopic method in some areas, are not detected in others and are present in the form of a "member-like material" in others. In the light of these data, it can be imagined that there are variants of the structure not only of the endothelium, but also of basement membranes, namely basement membranes with a poorly developed microfibrillar component. Only the first ones will be detected electron-microscopically. The disappearance of the microfibrillar component and the change in the ultrastructure of the basement membrane are well traced in the glomerular capillaries of normal animals. Thus, in the glomerular filter area, the basement membrane has a typical structure, one can even say, an emphatically typical structure in relation to the development of the microfibrillar component. At the same time, in the mesangial region, the typical basement membrane of the glomerular capillary is replaced by a loose substance with a reduced electron-optical density, and sometimes it appears that there is direct contact between mesangial cells and blood (Kurz, 1967; Farquhar, Palade, 1962). In fact,

this contact must be largely excluded by the basic substance described. The study of basement membranes under various types of pathology and pathogenic influences has made it possible to obtain a lot of data on the possibility of their transition from a typical form to a granular, homogeneous, and even "invisible" one (A. I. Smirnova-Zamkova, 1955, and others). Similar changes in basement membranes were detected electron-microscopically during X-ray irradiation of animals (O. V. Alekseev, 1968). It is clear that the essence of these transitions is a change in the form of organization of the basic substance of connective tissue, including basement membranes. The above facts indicate a high probability of the existence of the main substance, and not blood plasma, in the Disse space. Using the electron microscopic method, we have indeed detected in the Disse space and transendothelial hatches an accumulation of a substance similar to the material of cell coatings (O. V. Alekseev, 1968). This substance was detected in those areas where cell coatings were also found at the same time. Similar results were obtained in the examination of the spleen. Given the ability of cells to concentrate substances before they are absorbed, it can be said that quantitatively this process of extracting substances from the blood at the level of the wall can be very efficient. Absorbed substances are retained by the cells for a long time or are destroyed by them. Particles and macromolecules are also extracted directly from the perisinusoidal space where they have penetrated. It can be concluded that the barrier effect of the sinus and sinusoid walls is determined by a combination of structural and functional factors: the presence of the endothelial lining as such (limitation of the area of facilitated penetration), the main substance of the intercellular spaces and the perisinusoidal space, and the high absorption capacity of the reticulo-endothelial lining.

Structural and Functional Equivalents and Problems of Classification of Blood Capillaries

Electron microscopic studies, purely morphological and in combination with the labeled vessel method, have shown that the organ gradient of vascular permeability is due to differences in the fine structure of blood microvessels, especially their endothelial lining. These differences, in turn, are related to the functional and structural features of the corresponding organs, to general differences in the architectonics of microcirculatory networks, and to differences in hemodynamics. The study of the ultrastructural organization of the pathways and mechanisms of transcapillary exchange leads to the conclusion that the ultrastructural equivalents of large and small pores of physiologists change depending on the type of endothelium. For example, in microvessels with a continuous endothelium, the equivalent of small pores are inter-endothelial clefts, more precisely, sections of these slits in the area of intercellular contact, where their greatest narrowing is observed, as well as chains of microvesicles opening into each other

through narrow mouths. The latter equivalent is dynamic, probabilistic, and its contribution to transcapillary exchange is not quantifiable. In fenestrated endothelial capillaries, another equivalent of small pores appears, namely the diaphragms of the fenestra and the diaphragm microtubules. The permeability of the diaphragm is much higher than that of the intercellular clefts, and therefore the functional value of the latter in fenestrated capillaries is reduced. In the wall of sinuses and sinusoids, small pores are also detected by physiological methods, but their role in transcapillary exchange is very small. The equivalents of small pores here are the intercellular clefts and diaphragms, which are most likely different in their structure and permeability from the diaphragms in typical fenestrated capillaries. Continuous endothelial capillaries do not have the structural equivalents of physiologists' large pores. The functional equivalent of these pores here is microvesicular transport. In fenestrated or porous capillaries, the equivalent of large pores are transendothelial pores formed from fenesters. Two mechanisms of fenestra and pore formation are suggested: a) on the basis of microvesiculation and b) as a consequence of saucer-shaped depressions in thinned areas of the endothelium. In sinuses and sinusoids, the structural equivalents of large pores are primarily intercellular hatches (up to 10 μm in diameter) as well as transendothelial pores. The specific gravity of large and small pores in transcapillary exchange changes towards the predominance of the role of large pores (and their equivalents) in the transition from capillaries with continuous endothelium to sinuses and sinusoids. Therefore, it can be said that the organ gradient of vascular permeability is based on the ratio of large and small pores. Structurally, the abrupt changes in the ratios between these types of pores are due not so much to quantitative indicators as to qualitative ones. Given that morphology and function merge at the ultrastructural level, we believe that the fine structure of the equivalents of large and small pores can be chosen as a criterion for the functional-morphological classification of blood capillaries. According to this criterion, first of all, it is necessary to distinguish capillaries with the lowest permeability, excluding substances with a molecular weight of more than 40 OOO (according to some data, up to 2000) from transcapillary metabolism. The high barrier properties of these capillaries are due to the underdevelopment of microvesicular transport and the presence of continuous dense intercellular contacts (zonula occludens). These are cerebral capillaries, and possibly capillaries of some other organs and tissues. And the second group consists of capillaries, the walls of which allow both micromolecules and macromolecules to pass through. The basis for this is the absence of continuous belts of intercellular contacts, represented by either intermittent contact zones (zonula occludens punctiforma) or point contacts (macula occludens), as well as the relatively high activity of microvesicular transport. This group includes capillaries of skeletal muscles,

myocardium, lungs, various tissue membranes, membranes, etc. The third and fourth groups are represented by close, but still differing in their permeability: fenestrated (third group) and perforated (fourth group). The permeability of both is determined mainly by the permeability of related structures, such as fenestra and pores, as well as by the permeability of the basement membrane. In a large percentage of cases, fenestra and pores are present in the capillaries at the same time, which makes it necessary to distinguish an intermediate type. We see the need to distinguish between the third and fourth types in the fact that the diaphragms of fenestra are equivalent to small pores, so that the fenestrated capillaries proper (for example, in the intestinal wall of rats) differ significantly in their permeability from perforated and mixed capillaries. It should be noted that in one and the same organ in different species of animals there may be predominantly fenestrated or perforated capillaries. The fifth group includes sinuses and sinusoids, the endothelial lining of which forms intercellular and transendothelial hatches, which determine the highest permeability of these microvessels compared to the previous types. This high permeability allows the relevant authorities to exercise strict control over the macromolecular and cellular composition of the blood. The barrier or protective action of the sinus and sinusoid walls relies more on the functional activity of the reticuloendothelial lining than on the structure of the wall. From the above classification, it can be seen that two mechanisms are used for the structural regulation of transcapillary metabolism and its adaptation in accordance with the needs of a particular organ in the animal body: a) reformation of the transendothelial pathway and b) expansion of intercellular channels. The reformation of the transendothelial pathway is carried out in the following sequence: microvesiculation — fenestration — perforation — appearance of transendothelial hatches. All these structural transitions are associated with cell surface activity and are related forms of organization of transendothelial transport of macromolecules. The intercellular channels are less variable: supermicropores (type 1), micropores (types 2-4), and interendothelial hatches (type 5), i.e., there is only one qualitative transition (micropores-hatches). This indicates the conservatism of this pathway, due to the stability of intercellular contacts. Hence, it is logical to assume that under experimental influences that cause changes in vascular permeability, these changes are primarily due to reformations of the transendothelial pathway in the direction from increased microvesiculation to the formation of pores and hatches. With more serious impacts, a qualitative transition in the zone of intercellular contacts with the formation of intercellular hatches is possible. One indication of the validity of these assumptions is the hormonal transformation of the continuous endothelium into a perforated endothelium, as discussed in the previous sections. Another confirmation is found in the mechanisms that determine the capillary permeability

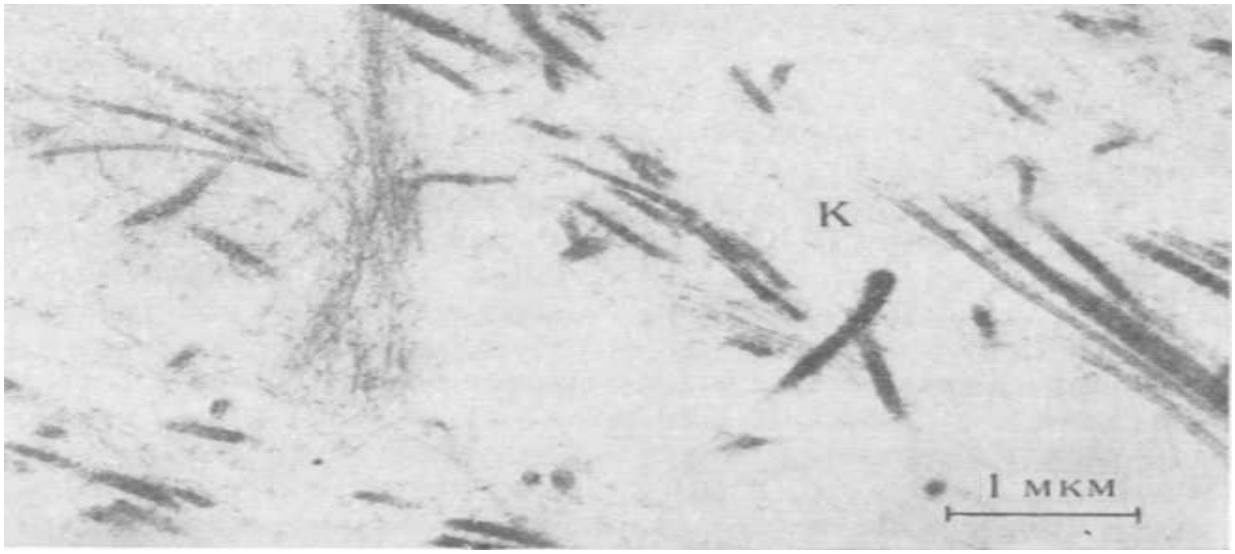
gradient. The foundations of this phenomenon are still poorly understood, which is explained by methodological difficulties (the need for strict electron microscopic differentiation of the arterial and venous ends of capillaries, the need for a comparative quantitative study of microvesicular elements under the condition of their uneven distribution in small areas of endothelial cells, etc.). Studies that have made a qualitative comparison of the arterial and venous ends of capillaries with continuous endothelium have shown that in some organs and tissues there is the appearance of fenestra and pores in the venous areas of the capillaries. Quantitative study of the same regions in capillaries with perforated endothelium revealed an increase in the number of pores in venous sites (Casley-Smith, 1970; Casley-Smith, 1970). Fenestra and pores appear only in areas where the endothelium is extremely thin (up to 80 nm or less). However, the thinning factor is favorable for the appearance of fenesters, but not decisive, since it is known that in alveolar capillaries the thickness of the endothelium can reach 80 nm (O. V. Alekseev, 1968), but pores are not formed. In this regard, it should be noted that the number of microvesicles in these capillaries is also reduced. For the final solution of the problem of the capillary permeability gradient, it is necessary to clarify the universality of this phenomenon and to conduct systematic comparative and quantitative studies of the arterial and venous parts of capillary microvessels under normal conditions and under experimental exposure.

Ultrastructural organization of perivascular transport

After overcoming the barrier in the form of a capillary wall, substances enter the perivascular space. What is their further fate? By what paths and by what mechanisms do they reach parenchymal cells in various organs? What is their path from the capillary wall to the lymphatic capillaries? All these questions and many others constitute the problem of pericapillary transport and interstitial (interstitial) circulation. It is clear that this problem is directly related to the problem of microcirculation, especially to the problem of transcapillary exchange. In many cases, the volumetric and linear rate of transport of substances through the vascular wall is determined by the rate of their outflow from the capillary wall, which supports certain concentration gradients. Electron microscopic studies of perivascular transport are just beginning. There are no special methods, no methodology has been developed. However, ideas are already being formed, trends and possible paths of development are outlined. The first conclusion that can be drawn from the general data on the ultrastructure of organs and tissues is the recognition of the unequal role of the perivascular space and interstitial tissue in the organization of hematotissue metabolism. This disparity is determined by the difference in the spatial relationships between specialized tissue cells and microvessels. For example, in the liver, liver cells have almost direct contact with blood plasma, and the penetration of substances from

the blood into the bile capillaries depends not on the permeability of the intra-organ connective tissue, but on the density of contacts between the liver cells themselves (Matter e.a., 1969). In this organ, it can be assumed that the interstitial flows of substances are organized quite simply: penetration from the blood into the space of Disse; diffusion and, probably, convection redistribution of substances along the vascular wall; In organs rich in connective tissue, the relationship between blood microvessels and specialized cells is much more complicated, although to varying degrees. In skeletal muscle, for example, the capillary "works" directly on the muscle fiber with one side and predominantly on the interstitium with the other. But even in the first case, between the capillary wall and the fiber, there is often not a homogeneous medium, but a highly structured system of various fibrillar elements immersed in a homogeneous matrix (basic substance). The fibrillar elements here not only form various networks, but also create formed strands that have one or another direction: directly to the muscle fiber, at different angles to it, along the vascular wall and away from the fiber. Such heavy structures are built from both typical collagen fibers (collagen bundles) and various microfibers. If we assume that they are similar not only in form but also in function to a wick, then it must be admitted that the proximity of the capillary wall to the muscle fiber does not determine the nature and size of the path passed by a particular substance from the vessel to the fiber. Such "fiber pipelines" could also carry out preferential or selective transport of substances through the interstitium, facilitating and accelerating their penetration, for example, through selective adsorption. It is known that various properties of fibrillar components of connective tissue are regulated by both local factors and neurohumoral influences (A. I. Smirnova-Zamkova, 1955, et al.). This can be the basis for the regulation of the transport of substances by fibrillar systems. Mechanical shifts in the organ (relaxation-contraction) are also likely to have an effect, changing the shape of the cords and their direction. In the conditions of pathology, when there is a disorganization of fibrillar systems as a result of destructive processes and their unregulated neoplasm, the resulting disorders of tissue trophism may be due to some extent damage to the pormal pathways of pericapillary and interstitial transport of substances. In this case, the substances, having left the vessel, fall into the labyrinth of multidirectional flows and, bypassing specialized cells, are dumped back into the bloodstream or lymphatic system. Such an interstitial (into the lymph) or perivascular (into the bloodstream) shunt will undoubtedly adversely affect the nutrition of the cells. In some vascular areas, there are favorable conditions for this. These conditions are the close location of arterial and venous microvessels, blood and lymphatic vessels. An illustration can be found in the papillary capillaries of the skin, where the arterial and venous knees of the capillary loops are almost adjacent to each other. It is possible that an interstitial arteriovenous shunt in these

conditions is excluded by a well-developed fibrillar system (drainage system) and a reinforced basement membrane. It is also possible that it is the damage to the normal organization of this system in the skin that is one of the basis for its abrupt change in collagenosis. The importance of the questions raised makes it necessary to proceed directly to the study of the role of fibrillar elements of connective tissue in the spatial organization of interstitial transport routes and the actual transport of certain substances. The study of the ultrastructure and physicochemical properties of interstitial connective tissue from this point of view, which has recently emerged (Sgope, 1972; Laurent, 1972; Mendler, 1972; Merker and Cunther, 1972) will provide extensive and valuable information, but the final solution to the problem obviously lies in the field of functional ultrastructural methods. Single studies carried out with the help of a light microscope have shown that the dyes, having left the vessels, do not spread into the tissues diffusely, but in accordance with the course of the fibrous ones. At the ultrastructural level, it is interesting to observe that exogenous peroxidase, once in the tissue, is detected in an increased amount among collagen fibers (Zacks and Saito, 1969). Substances of different nature (paints, peroxidase, glycogen granules, iron oxide saccharate), different in the size of molecules and particles (from 3 nm — sacrate, to 30 nm — glycogen granules) have an affinity for collagen bundles. Observations with glycogen and iron oxide saccharate suggested that this transport is bilateral: to and from the vessels. Apparently, in different bundles, transport goes in different directions. By analogy with arterial and venous vessels, these bundles can be designated as arterial (transport from the vessel to the tissue) and as venous (from the tissue to the vessels, obviously to the venous vessels). Studies carried out in this direction allow us to make only a number of assumptions regarding the structural organization of interstitial transport of substances and the role of fibrillar elements of connective tissue in this process. The need for new and broader research on these issues is clear.

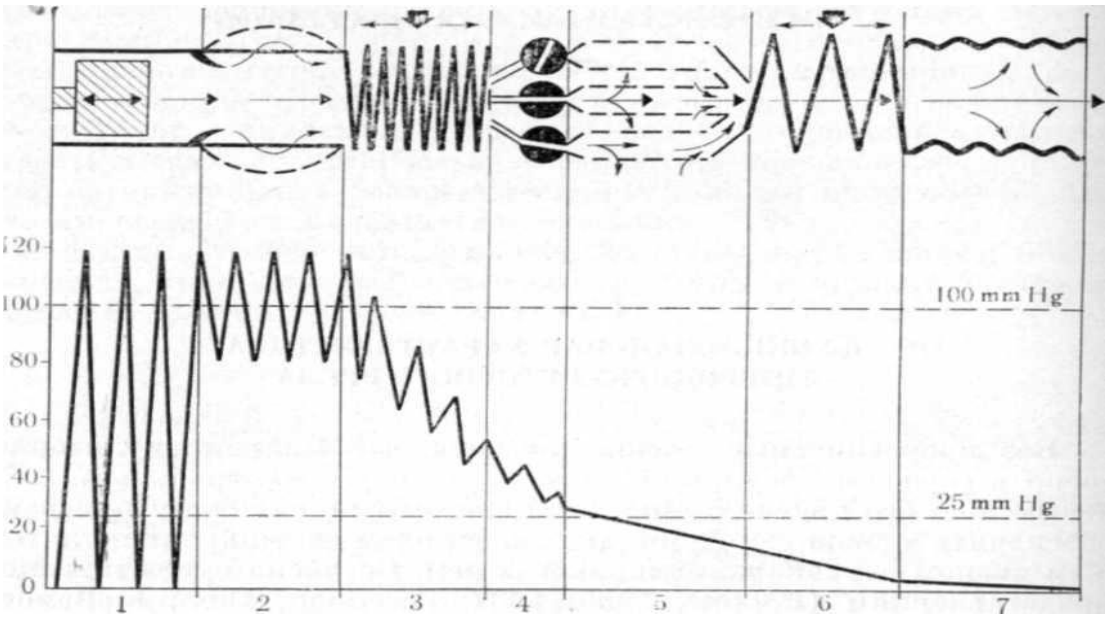


Picture. 6 Section of the lymphatic capillary wall
K – collagen fibers and the lumen of the lymphatic capillary.

Lymphatic capillaries, the walls of which are also formed by the endothelium, evacuate excess fluid, protein molecules and metabolic products from the tissues. Compared to blood capillaries, lymphatic capillaries have a large lumen (10–100 μm, average 20–40 μm) formed by a thinned endothelial lining. About 2 liters of fluid flow through the lymphatic vessels (Figure 6). A characteristic feature of lymphatic capillaries is the presence of specialized structures that "bind" the capillaries to the adjacent connective tissue.

The functional features of the lymphatic capillary wall are determined mainly by the mobility of intercellular contacts in the endothelium. Capillaries are the thinnest vessels, 5–7 μm in diameter and 0.5–1.1 mm long. For example, the heart has 2 times more capillaries per 1 mm2 cross-section than skeletal muscle. In the gray matter of the brain, where there are many cellular elements, the capillary network is much denser. than in white. There are two types of functioning capillaries. Some of them form the shortest path between arterioles and venules (main capillaries). Others are lateral branches of the former: they branch off from the arterial end of the main capillaries and flow into their venous end. These lateral branches form capillary networks. The volumetric and linear velocity of blood flow in the main capillaries is greater than in the lateral branches. The great capillaries play an important role in the distribution of blood in the capillary networks and in other microcirculation phenomena. The blood pressure in the capillaries is measured directly: under the control of a binocular microscope, a very thin cannula connected to an electromanometer is inserted into the capillary. In humans, the pressure at the arterial end of the capillary is 32 mm Hg, and at the venous end it is Hg, and at the top of the capillary loop of the nail bed it is Hg. In the capillaries of the renal glomeruli, the pressure reaches 65 mmHg, and in the capillaries entwining the renal tubules, it is only 14–18 mm Hg. The pressure in the capillaries of the lungs is very low – on average Hg. Capillary pressure is measured in a position where the capillaries of the area to be examined are at the same level as the heart. In the case of dilation of the arterioles, the pressure in the capillaries increases, and in the case of narrowing, it decreases. Blood flows only in the "standby" capillaries. Some of the capillaries are cut off from circulation. During the period of intensive activity of the organs (for example, during muscle contraction or secretory activity of the glands), when the metabolism in them increases, the number of functioning capillaries increases significantly. The regulation of capillary circulation by the nervous system and the influence of physiologically active substances—hormones and metabolites—on it are carried out by their action on arteries and arterioles. Narrowing or dilation of the arteries and arterioles alters both the number of functioning capillaries, the distribution of blood in the branching capillary network, and the

composition of the blood flowing through the capillaries, i.e., the ratio of red blood cells to plasma. In this case, the total blood flow through the metaarterioles and capillaries is determined by the contraction of the smooth muscle cells of the arterioles, and the degree of contraction of the precapillary sphincters (smooth muscle cells located at the mouth of the capillary when it departs from the metaarterioles) determines how much of the blood will pass through the true capillaries. In some areas of the body, such as the skin, lungs and kidneys, there are direct connections of arterioles and venules – arteriovenous anastomoses. This is the shortest route between arterioles and venules. Under normal conditions, the anastomoses are closed and blood passes through the capillary network. If the anastomoses are opened, some of the blood can flow into the veins, bypassing the capillaries. Arteriovenous anastomoses act as shunts that regulate capillary circulation. An example of this is the change in capillary circulation in the skin when the ambient temperature rises (above 35°C) or decreases (below 15°C). Anastomoses in the skin open and establish blood flow from the arterioles directly to the veins, which plays an important role in thermoregulation processes. The structural and functional unit 15 mm24xmm70 of blood flow in small vessels is the vascular module, a relatively hemodynamically isolated complex of microvessels that supplies blood to a certain cell population of an organ. At the same time, there is a specificity of vascularization of tissues of various organs, which is manifested in the peculiarities of branching of microvessels, density of capillarization of tissues, etc. The presence of modules allows you to regulate local blood flow in individual micro-areas of tissues. In addition to the above-mentioned vessels, it has been proved that arteriolovenular anastomoses, which are present in all organs and represent the pathways of shortened arterial blood flow into the venous bed, bypassing the capillaries, belong to the microcirculatory bed. These anastomoses are divided into true anastomoses, or shunts (with and without obturator devices capable of blocking the flow of blood), and interarterioles, or semi-shunts. Due to the presence of arteriolovenular anastomoses, the terminal blood flow is divided into two pathways of blood movement: 1*) transcapillary, which serves for metabolism, and 2) extracapillary* juxtacapillary (from the Latin juxta – near, near) blood flow, which is necessary for the regulation of hemodynamic equilibrium; The latter is due to the presence of direct connections (shunts) between the arteries and veins (arteriovenous anastomoses) and arterioles and venules (arteriovenular anastomoses).



Picture. 7. Scheme of the divisions of the circulatory system

Due to extracapillary blood flow, if necessary, the capillary bed is unloaded and blood transport in the organ or given area of the body is accelerated.

It's like a special form of roundabout, collateral, blood circulation. The main driving force that delivers blood to the tissues and ensures the movement of interstitial fluid and lymph is the propulsive activity of the heart.

Blood, as a complex system, has rheological properties that significantly distinguish it from other fluids. Hemodynamic conditions in the microcirculation system are influenced not only by the structural mechanisms of the microcirculatory bed, but also by the aggregate state of the blood, the interaction between the formed elements and the circulating plasma. Hemodynamic parameters in microvessels are closely related to the permeability of their walls, and the latter reflects force gradients and protein concentrations in the interstitium. In turn, the conditions existing in the interstitial environment of the lymphatic capillaries form the mechanisms of lymph formation and lymph advancement. Microcirculation, as the main system integrating the vital activity of tissues, is regulated mainly by local control mechanisms, such as mediator and myogenic. Nervous and humoral influences are realized at the level of the smooth muscular apparatus of resistive microvessels and in the contraction of endothelial cells. In the activity of the microcirculation system, the principle of self-regulation is very effectively manifested, according to which changes in functional parameters in each of the three compartments and at the boundaries between them significantly affect transport phenomena in neighboring compartments. The self-regulating mechanism ensures, among other things, the protection of tissues from excessive fluid intake and accumulation. The insufficiency of any link of this

mechanism and the inability to compensate for it leads to tissue edema, one of the most common syndromes in many pathological conditions.

The velocity of blood flow in the capillaries usually does not exceed 1 mm/s, and erythrocytes move slightly faster than plasma. Hydrostatic pressure in capillary-type vessels in different organs is recorded in the range of 18-40 mm Hg. As a rule, it is slightly higher than the colloidal-osmotic pressure of plasma proteins (19-21 mm Hg), due to which the pressure gradient through the capillary walls is directed towards the tissue and the filtration of the fluid dominates over its reabsorption into the plasma. The excess volume of fluid entering the tissue is reabsorbed by the roots of the lymphatic system or used to form secretions, for example, in the digestive glands. The hydraulic conductivity of the walls of blood microvessels, i.e. permeability to water, varies depending on their nature (arterial or venous capillaries, venules) and organ affiliation.
The value of the hydrostatic pressure of the interstitial fluid (in the intercellular space) is usually estimated as close to zero, i.e. not much different from the value of atmospheric pressure.
Along with ensuring the processes of metabolism between plasma (lymph) and the working elements of the tissue, a microcirculation system. It also performs other functions that are vital for the normal functioning of the body. The total mass of endothelial cells in the adult human body reaches 1.5-2 kg, and the size of the cell surface is generally extraordinary, apparently close to 1,000 m2. A number of important biochemical reactions take place on this vast surface, such as the conversion of the inactive form of angiotensin I into the active form of angiotensin II.
The role of the endothelium in the synthesis of prostaglandins, especially prostacyclin, which supports thromboresistance of the endothelial surface, is extremely important.

FACTORS OF LOCAL AND HUMORAL REGULATION OF THE MICROCIRCULATORY BED

The normal tuning of the microcirculation system, which determines the optimal blood flow in the capillaries, and therefore the normal transcapillary exchange between blood and tissues, is provided by two regulatory systems – local, humoral and nervous – and their interaction. An important role here is played by the own autoregulation of the microcirculatory system, which manifests itself in the spontaneous activity of smooth muscle cells, the rhythm of which is superimposed by the rhythm of external regulatory influences.

Microvascular reactivity

In our opinion, it is expedient to begin the presentation of materials related to the regulation of microcirculation with the consideration of the reactivity of microvessels, and then proceed to the description of the "reactogenicity" of regulators, local and neurogenic. It is the differences in

reactivity that can be the basis for the fact that the same regulators have different effects on certain parts of the microcirculatory bed, causing disagreements in assessing the effect of their action. The reactivity of microvessels is due to the main property of smooth muscle cells, t**.** Their ability to contract and relax. At the same time, the reactivity of microvessels refers to the degree of their sensitivity to various agents that affect muscle cells. The reactivity of capillaries without muscle cells is usually understood as the degree of change in permeability under the influence of various influences. The sensitivity of muscle cells of microvessels, in particular to some vasoactive substances, is significantly higher than that of large vessels; dose, It causes a reaction of muscle cells of microvessels, 10-100 times smaller. To record the observed effect, it is necessary to measure the diameter of the microvessels, but due to the small size, for example, of the precapillary sphincter or metaarteriole (diameter 10–20 μm), it is difficult to perform it with a high degree of accuracy. Even more difficult is determining the speed of blood flow or the amount of blood flowing in these vessels. Nevertheless, methodologies have been developed to allow such measurements to be made. Experiments have shown that the precapillary sphincters are the most sensitive to the action of both constricting and expanding agents. The presence of a sensitivity gradient on the microvascular arterial bed of the rat was found from a threshold value of epinephrine concentration of 1:6 million for the precapillary sphincter to 1**:**500,000 for terminal arterioles. A similar gradient of reactivity has been found with respect to electrical stimulation The gradient of reactivity changes or even disappears depending on the structural organization of the microvasculature bed in different organs and tissues. Therefore, in such a Tissues, such as the skin, where the precapillaries branch directly from the comparatively large arterioles, have almost no gradient of reactivity. When the microcirculatory bed is affected by vasoconstrictors, the sequence of response of vascular components is as follows: the precapillary sphincters are the first to close, then the lumen of the central canals decreases and the muscle venules are the last to narrow. When vasodilators such as histamine are used, the microvessels react in the opposite order. The described scheme is largely arbitrary. Such a picture is observed mainly on the microvessels of the mesentery, provided that the dose of the vasoactive drug is correctly selected. At high doses of the applied substance and on other microcirculatory objects (skin, lungs, spleen, liver, muscles), a different pattern in the response of microvessels is observed. Under conditions of pathology, the sensitivity of microvessels to vasoactive substances changes. For example, on the microvessels of the canine mesentery, it has been shown that in the phase of compensation for hemorrhagic shock (arterial pressure 70-50 mm Hg) it is characterized by closure of the precapillary sphincters, contraction of the central canals, and a decrease in capillary blood circulation. During this period, there is a sharp increase in the

sensitivity of the microcirculatory bed to adrenaline. In the phase of decompensation (arterial pressure 45-35 mm Hg), the sphincters and central channels dilate, hyperemia of the capillary bed develops, and blood flow slows down. The ability of smooth muscle cells to contract is dramatically reduced (Chambers and Zweifach, 1947; Shorr, 1950; Zweifach, 1952). Increased sensitivity of microvessels to vasopressor substances during hemorrhagic hypotension has also been shown in the works of other authors (Gray, 1971). The reactivity of microvessels is not the same in different organs and tissues. This pattern is especially evident in relation to adrenaline. The microvessels of the skin are highly sensitive to adrenaline compared to the reactivity of some other organs. From them it is clearly evident that vascular smooth muscles differ in their readiness to react to the action of biologically active substances, and these differences exist both within the same microcirculatory network and in the same parts of different networks: local and organ gradients of reactivity, respectively.

Effects of vasoactive substances

Histamine is one of the most active vasodilators. The main reserves of endogenous histamine in humans and animals are localized in mast cells of connective tissue and in basophilic leukocytes. The high physiological activity of histamine and polyfunctionality seem to be due to the fact that it is normally present not only in leukocytes, endothelial and smooth muscle cells, but also in the cells of all other organs and tissues. Under pathological conditions, normal histamine metabolism It can be disrupted, which leads to its accumulation in the tissues, and this causes various disorders from allergies to the so-called histamine shock. The release of histamine into the surrounding tissue occurs as a result of mast cell degranulation, although it has been shown that histamine and serotonin can be released without disrupting the morphological integrity of the mast cell membrane. Histamine liberators are protein substances of an antigenic nature: egg white, polymyxin, as well as a number of synthetic preparations, for example, 48/80 and 19352. As early as 1919. Dale and Richard have shown that, in contrast to its constrictor effect on large blood vessels, histamine in comparatively high doses causes dilation of the smallest vessels. Due to its active vasodilatory effect and ability to increase the permeability of the vascular wall, some researchers assign histamine a leading role in the formation of the vascular phase of inflammation. The study of the vasoactive effect of histamine was mainly carried out in animal experiments using various methods of administration (intravascular administration, injection, iontophoresis and local application). The latter form and microinjection are the most appropriate ways of using histamine in the study of its effects on microvessels, since intravascular administration may cause secondary phenomena associated with changes in general haemodynamics (Lee 1957). Intravital observations on the microvessels

of the cat's lungs have shown that intravenous administration of histamine causes the "disappearance" of capillaries and arterioles due to spasm of the arteries (Wearn e. a., 1934). Local application of histamine to the mesentery of a rat at a concentration of 1:100 was accompanied by rapid dilatation of all muscle vessels, and at higher dilutions only the metarterioles and precapillary sphincters dilate (Chambers and Zweifach, 1944). Topical application or intravenous administration of histamine resulted in dilatation of the sinuses and slowing of blood flow in them, as shown by biomicroscopy of the liver of animals (Seneviratne, 1950). Intravenous administration of histamine to guinea pigs causes a sharp contraction of not only pulmonary arterioles but also venules in 60% of animals, which confirms histological observations about the strong development of the muscle layer in pulmonary venules (Irwin et al., 1954). In the development of histamine shock in guinea pigs, intravital studies have established that at first there is a widespread contraction of arterioles and venules, which is then replaced by short-term vasodilation and acceleration of blood flow. This is followed by a general slowing of blood flow and erythrocyte aggregation phenomena with the formation of white blood clots and bleeding. In anaphylactic shock, similar changes are noted. A lethal dose of the antigen causes maximum contraction of the muscular parts of the terminal bed of the lungs, which are macroscopically pale in color (Irwin et al., 1955). Local application of histamine (1:1000) to the human oral mucosa was accompanied by marked dilatation of microvessels (Franke, 1964). Intravenous administration or topical application of histamine caused impaired blood flow in the microvessels of the rabbit's nasal mucosa and the formation of white emboli and thrombi (Neuman 1961). Topical application of histamine to the mesentery of cats, dogs, and rabbits J. S. Lee (1957) observed significant dilatation of vessels less than 50 μm in diameter. The author notes that the threshold of sensitivity to histamine under local action in mesenteric microvessels is lower than in small cutaneous arteries. According to some authors, the histamine-like effect of local application of endotoxin (100 μg) on the microvessels of the hamster buccal sac, observed by biomicroscopy (Litton, 1969), can be explained not by the direct effect of endotoxin on the vessel wall, but by the release of vasoactive substances such as histamine, serotonin, bradykinin, etc. (Vick, 1964). Our studies on rat mesenteric microvessels have shown that the application of histamine (100 mg in 0.1 ml) is accompanied by a reaction of "enlightenment" and even "disappearance" of the microvessels, which is probably explained by a sharp decrease in blood filling as a result of constriction of the supply artery. The vasodilatory effect of histamine has been observed by many authors on the mesentery of the rat (Zweifach, 1953; Weiner, 1967; Altura, 1968; Baez, 1969), on the microvessels of the hamster cheek sac (Litton et al., 1967) and other objects. In experiments on the mesentery of rats, for example, it was shown

that the application of histamine (3 μg in 0.1 ml of saline) causes dilation of terminal vessels with a latency period of 5-10 s and a duration of 70-80 s. Application of histamine liberators (preparation 48/80 of polymyxin B) also caused dilation of the vessels and an increase in blood flow in the capillary network. The vasodilatory effect of liberators was evident in 3–5 s and lasted 3–4 min. No synergy between 48/80 and histamine was observed (Weiner, 1967). In this regard, it should be noted that serotonin as a histamine liberator is 100 times less active than the 48/80 drug (Feldberg and Smith, 1953). In contrast to the data obtained in the mesentery, topical application of 48/80 caused contraction of the arterioles (diameter 18–54 μm) of the soft meninges of mice (Rosenblum, 1973). Somewhat different from these data are the results obtained with a titanium chamber implanted in the abdominal wall of a rabbit in such a way that biomicroscopy of the vessels of the mesentery of the duodenum can be carried out (Heisig and Siemseen, 1967). The authors observed no changes in blood pressure, changes in heart rate, or changes in blood flow in macrovessels with intravenous histamine (4 to 30 μg/kg per minute). With an increase in the dose of histamine (100-500 μg/kg per minute), blood pressure decreased, blood flow slowed down, and death occurred, but neither constriction nor dilatation of microvessels was noted. On the mesentery of a rat, it has been shown that intra-arterial and topical application of histamine and (5-histidine) inhibits the constriction of arterioles caused by epinephrine and norepinephrine (Baez, 1969). Histamine does not appear to affect the adhesive properties of leukocytes: no increase in the number of leukocytes was observed when counting leukocytes moving along the vessel wall through a selected point of the visual field on the microvessels of the mouse mesentery and the buccal sac of the hamster Atherton and Born (1972). In irradiated animals, D. S. Maruev (1972) noted an increase in the sensitivity of the terminal vessels of the lungs to histamine in the first hours after radiation exposure, a weakening of the dilatorial effect, and a sharp increase in the constrictor effect. Thus, these data indicate that the nature of the response of microvessels to histamine depends not only on the method of administration and dose, but also on the type and size of the vessel. It should also be emphasized that histamine predominantly affects the permeability of the endothelium of the venules, and the venules of the lungs and brain are less sensitive to it than, for example, the venules of muscle, skin, etc.

Serotonin (5-hydroxytryptamine) is also one of the physiologically active components found in mast cells. The data on the quantitative content of serotonin and histamine in mast cells in different laboratory animals are contradictory. At the same time, it has been shown that the content of serotonia, histamine and heparin is characterized by a ratio of 1:10:30 (Benditt e. A., 1955) and that 48/80 releases 10 times more histamine. than serotonia (Bhattaharya and Lewis,

1970). It is also assumed that there is no clear correlation between the amount of serotonia in tissue and the number of mast cells. In addition, it is believed that in humans and some animals (rabbits, cats, dogs), serotonin is not synthesized and does not accumulate in mast cells. However, the presence of serotonin in human mast cells has been proved relatively recently by Falk staining (G. P. Popova et al., 1969). Some authors believe that serotonin is a histamine liberator (Feldberg and Smith, 1953), while others have not observed the release of histamine from mast cells even when large doses of serotonia are administered (Rowley, Benditt, 1956). More detailed information on the physiological role of serotonia in the body can be found in the monograph by X. H. Planelles and 3. A. Popenenkova (1965) and E. A. Gromova (1966), and the pharmacology of serotonia and its antagonists was elucidated by I. I. Pidevich (1971). As for the effects of serotonia on the smooth muscle of blood vessels, the available data are not as definite as in the case of histamine. In experiments with perfusion with a constant volume of blood in a dog's limb, it was shown that the effect of serotonin depends on the initial tone of the peripheral vessels (Haddy et al., 1959). On the other hand, radioangiographic studies of rabbit lung vessels perfused with serotonin and reserpine have shown a pronounced constrictor effect (Virtama and Jankala 1961). However, most biomicroscopic experimental work suggests that serotonin should be considered predominantly as a terminal vessel constrictor. For example, the constrictor effect of subthreshold doses of serotonia (0.1–0.01 μg/ml) on microvessels in the buccal sac of a hamster was clearly revealed by biomicroscopy (Akers, Zweifach, 1955). Similar data on the same object were obtained by other researchers (Litton e. a., 1967). According to Altura (1967), the application of serotonin (5 μg in 0.1 ml) to the surface of the rat mesentery caused constriction of the muscle vessels, which progressed from the venular to the arterial part of the microvasculature. The use of adrenergic blockers did not alter the constrictor effect of serotonin, and in a number of experiments potentiated its effect. Venular constriction developed 40-45 s after the application of the drug. A significantly higher dose of serotonia (40 μg in 0.1 mL) applied to the same object caused partial contraction of metaarterioles and precapillary sphincters and more pronounced contraction of venules. The maximum effect developed in 50-55 s and disappeared in 2 min. Application of the drug 48/80, which, along with histamine, releases serotonin from mast cells in a ratio of 10:1, causes extensive dilatation rather than constriction of the microvessels of the rat mesentery (Weiner, 1967). Serotonin, like histamine, has not only vasoactive properties, but also the ability (in large doses) to damage the endothelium, causing it to swell and change its permeability. In this regard, the most vulnerable are the muscular venules, where the most favorable conditions for the formation of white platelet and leukocyte thrombi occur. Under the influence of serotonin, the sensitivity of microvessels to

adrenaline and norepinephrine increases, and the phagocytic properties of the endothelium are stimulated.

Bradykinin is a highly active vasodilator in terms of its effect on microvessels. The threshold of its physiological action lies in the range of 10~6 g/ml. Bradykinin is formed in blood plasma and its half-life in humans is 0.1—0.6 minutes, which is explained by the high rate of inactivation by a specific plasma enzyme — kininase or carboxypeptidase. The effect of bradykinin on the microvessels of various organs and tissues is currently widely studied. However, there is no consensus on the nature of its effect on the microcirculatory bed. Some researchers have observed dilatation of microvessels under the action of bradykinin. Dilation of arterioles and venules leads to overflow of the microvasculature with blood and to a slowdown in blood flow in the venules, where the permeability of the vascular walls is particularly pronounced (Zweifach, 1964, 1966). Low doses of bradykinin (0.2 μg) clearly show dilatation of arterioles, opening of precapllar sphincters, and an increase in the number of functioning capillaries (Zweifach, 1966). Based on rheoplythysmographic studies on the fingers, it has been suggested that bradykinin closes arteriolo-venular shunts and improves capillary blood flow. The observed effect of bradykinin is consistent with changes characteristic of reactive hyperemia (Burch and De Pasquale, 1962). With the use of large doses of bradykinin (2–20 μg), qualitatively different microvascular reactions were observed: a pronounced marginal standing of leukocytes, their exit into the surrounding tissue (Zweifach, 1966). These changes were further followed by a slowdown in blood flow and the development of stasis. Intra-arterial perfusion of skeletal muscle and skin with bradykinin caused an increase in volumetric blood flow velocity (Heman and Paldino 1967). The ability of bradykinin to increase vascular permeability has been established by numerous studies. The permeability of the vascular wall of the venules and capillaries increases by a factor of 36 (Mouktar and Leger, 1964). However, the increase in the permeability of capillaries and venules is not accompanied by a change in their resistance or any signs of damage, although the release of fluorochrome-deprived protein from the vessels has taken place, as was established by intravital observations on the mesentery of rats using an ultraviolet microscope (Witte et al., 1961). Bradykinin dilates the vessels of the skin, skeletal muscles, upper and lower extremities, as well as the vessels of the spinal cord, brain, coronary vessels, and vessels of the sweat, saliva, breast, lacrimal and pancreatic glands. Skin vessels are more sensitive to bradykinia than muscle vessels. The vessels of the mesentery are even less sensitive (Hyman and Paldino, 1967). However, depending on the size of the dose and the route of administration, bradykinin can also cause a vasoconstrictor effect (Burch and De Pasquale, 1962), which is different in the vessels of different organs of the same organism. Intravenous

administration of bradykinin at a rate of 25 μg/kg per minute reduced the total peripheral vascular resistance, and organ vascular resistance changed in different ways: increased in the salivary glands, did not change in the skin and kidneys, decreased in the intestines, liver, spleen, pancreas, adrenal glands, in the brain, heart and lungs. This indicates the selective vasoconstrictor and vasodilatory effects of bradykinin (Arcidiacono E. A., 1967). Studies have shown that there is a synergy in the action of bradykinin and serotonin. For example, preliminary application of serotonin (200 μg in 0.1 ml of saline) on the microvessels of the rat mesentery (in lifetime conditions) followed by 10-15 seconds of bradykinin at the same dose caused an increase in the effect in the form of spasm of venules, stasis in capillaries, and rupture of blood vessels with hemorrhages. The synergy of the action of bradykinin with serotonin was confirmed by experiments with the preliminary use of adrejergic blockers phenoxybenzamine and chlorpromazine (Weiner and Altura, 1967). However, a pronounced synergy in the action of bradykinin with histamine on the cerebral vessels of monkeys could not be established (Walters, 1971). It is assumed that bradykinin selectively acts on smooth muscle cells in certain areas of the vascular bed. The mechanism of this action is associated with a change in the electrical potential (depolarization) of the cell membrane. On the mesentery of irradiated rats, it was shown that the sensitivity of microvessels to intravenous administration of bradykinin after irradiation increased by 25 times, and to histamine to an even greater extent (I. Y. Gaponyuk, T. N. Kalinkina, 1972). The drugs discussed — histamine, serotonin, bradykinin — make up a group of so-called mediators of acute inflammation. It should be emphasized here that all of them have high biological activity and a wide range of effects, both in terms of the effects they cause and in relation to the physiological processes that they can influence or in which they are directly involved. All this makes it necessary to consider them not only as regulators, but also as "modulators", specifically "staining" or distorting the action of other regulators of the state of blood vessels, for example, neurogenic. If we take into account the recent work on the significant influence of prostaglandins on the regulation of microcirculation (Messina E. A., 1971; Harrison, Wolf, 1972; Csepli, Erdelyi, 1972, et al.), the complexity of the biochemical processes that regulate blood distribution and blood flow velocity in the microcirculatory system becomes even clearer. Histamine, serotonin, bradykinin, as well as prostaglandins predominantly act where they are formed. The next group of regulators are those that act at a distance, i.e., those that are transported to the site of action by the blood. If the action of the former is more or less localized, then the action of the latter is rather systemic.

Vasopressin (Pitressin) It is one of the hormones of the posterior pituitary gland and, as the name indicates, has a pronounced vasoactivity, leading to vasocontraction and an increase in

blood pressure. Intravital observations on the microvessels of the lungs of frogs and cats have established that intravenous administration of the hormone, as a rule, causes contraction of arterioles and desolation of capillaries (Wearn e. a., 1934). At the same time, it is known that local and intravenous administration of the hormone is not accompanied by any changes in the vessels of the soft meninges of cats, rabbits and monkeys, although in some cases vasoconstriction has been noted on these objects. De Landen (1965), while studying the effect of vasopressin on peripheral circulation, found that some pathological conditions and processes (hypoglycemic coma, postoperative period, irreversible hemorrhagic shock, post-infectious period) are characterized by the opening of arteriolo-venular shunts. On this basis, he tries to explain the therapeutic effect of the use of vasopressin in these conditions by the closure of arteriolovenular shunts and the direction of increased blood flow through the capillary network that feeds the tissue. However, it is difficult to accept this explanation for the reason that such a statement requires direct visual observation of the behavior of anastomoses. Since such data are not available, the effect of pitressin may be attributed to an increase in systemic blood pressure. Intra-arterial administration of vasopressin at a dose of 0.02 U/kg caused a 70% increase in blood flow velocity and a 44% increase in pressure in the microvessels of the guinea pig's middle ear (Perlman E.A., 1963). decreasing the concentration to 0.02—0.03 units. There was a reduction in metarterioles, precapillaries, and venules, and a dose of 0.01 units caused a contraction of venules only. Intravenous administration (0.1 units) did not change blood pressure, but capillary circulation increased within 1-2 minutes, and an increase in the effect of threshold doses of epinephrine and norepinephrine (Altura e.a., H)65) was observed. On the dorso-trapezius muscle of a rat under lifetime conditions, it was shown by microscopy that a synthetic analogue of vasopressin injected into the jugular vein (0.05—0.8 μg/100 g of body weight) has various effects on pre- and postcapillary vessels, but all these changes are reduced to a decrease in capillary perfusion similar to that which occurs in the late post-hemorrhagic period at a blood pressure of 40 mm Hg. (Gray, 1971). -*t* The significance of the vasoconstrictor effect of vasopressin in the creation of a model of experimental myocardial infarction in rabbits was demonstrated in the experiments of Bicher and Beemer (1967). The authors showed that pre-administration of dextran (molecular weight 75 OOO) to healthy rabbits and subsequent (after 15 min) intravenous administration of vasopressin at a dose of 5 U/kg caused acute myocardial ischemia in 29 out of 33 animals, which was confirmed electrocardiographically (reduction of the interval $S - T$, T-wave inversion, block phenomena, arrhythmia) and on the section. A similar picture of myocardial ischemia was observed in 14 out of 16 rabbits with pre-induced atherosclerosis according to N. Anichkov and with subsequent administration of dextran. In the

Laboratory of General Pathophysiology and Experimental Therapy, experiments were also carried out to reproduce acute coronary circulation disorders by combined administration of high-molecular dextran (molecular weight 500,000) and vasopressin (5 U/kg). Intravenous administration of one dextran (0.5 g/kg) to rabbits caused intravascular aggregation of red blood cells, obstruction of blood flow and slowing of contractions. Intravenous vasopressin showed ECG changes (bradycardia, wave change T and spacing $S - T$, abnormal heart rhythm). Combined administration of dextran and vasopressin (after 15 min) increased the degree of erythrocyte aggregation and the development of venule stases. At the same time, coronary circulation was dramatically impaired, as evidenced by deeper and more persistent ECG changes than in the case of vasopressin injection alone. There were also changes in myocardial metabolism (A. M. Chernukh, M. D. Vakar, P. P. Aleksandrov, G. V. Chernysheva).

Angnotensin I and angiotensin II (deca- and octapeptides, respectively) have a pronounced hypertensive effect, especially angiotensin II. According to some data, angiotensin II causes contraction not only of smooth muscle cells, but also of endothelial cells, both when applied topically and when injected into the bloodstream (Robertson e.a., 1972). Other effects include the ability to directly and reflexively stimulate the release of adrenaline from the adrenal glands. facilitate synaptic adrenergic transmission, directly affect electrolyte transport (in doses that do not induce smooth muscle contraction) (Hornych e. a., 1973). Interesting biochemical relationships between angiotensin and bradykinin have been revealed. Igic et al. (1971) showed that the lungs of dogs and rats contain the enzyme kininase P., which inactivates bradykinin and simultaneously converts apgnotensin I into angiotensin II. Apparently, there are many such points, critical or turning points, on the way from the initial regulatory response to the final sustained effect. From the presented materials it is clear that in a long series (a full description of it is beyond our task) of chemical regulators of microcirculation there are groups of substances of the same type in their effect and in this respect seem to be able to replace or repeat each other. However, this is hardly a way to increase the reliability of regulation. In our view, there is a deeper meaning in this fact. Indeed, all regulators of the same type have an equal effect only on microcirculation. At the same time, they differ significantly in their participation in the regulation of other tissue systems and physiological processes. The material support of these different systems and processes often requires the same type of response on the part of the microcirculatory system. Perhaps because one and the same regulator "spurs" a particular process with one end and adjusts the microcirculation accordingly with the other. Thus, the regulation of interstitial processes and their material support can be carried out simultaneously and economically: one regulator is used for two actions. It is clear that some of these regulators

have similar relationships with the microcirculatory system, but this similarity does not make them twins, although it does make it difficult to elucidate their true physiological role.

Effects of neurotransmitters

Such "concomitancy" is most developed in neurotransmitters: acetylcholine, adrenaline and norepinephrine, which act on a variety of systems. It is quite understandable that only on the basis of such universal regulators could a universal regulatory system, namely the nervous system, be formed.

Epinephrine and norepinephrine have an intense vasoconstrictor effect. It has been found on mesenteric microvessels (Altura, Zweifach, 1967; Baez, 1969; Vacek, 1969; Al-tura, 1971), the cheek pouch of a hamster (Dulind E. a., 1968; Litton et al., 1969), lungs (D. S. Maruev, 1972; Hall, 1925; Wearn e. a., 1934), liver (Wakim, 1942), pancreas (Berg, 1930), skeletal muscle (Gray, 1971), pituitary soft lining (Worthington, 1960), human oral mucosa (Franke, 1964), human nail bed and bulboconjunctiva (Davis, Landau, 1966, 1967). It should be noted that the constrictor effect of epinephrine on the microvessels of various organs and tissues is manifested both by intravenous administration and by local administration of the drug. In addition, Some authors emphasize an increase in sensitivity to adrenaline in conditions of pathology, for example, in arterial hypertension. For example, in rats with renal hypertension, hyperplasia of the capillary bed with vascular neoplasm and an increase in the degree of their tortuosity was observed. At the same time, there was an increase in the sensitivity of arterioles and precapillary sphincters to adrenaline. The morphological changes described were absent in rats with hypertension induced by administration of deoxycorticosteronacetate in combination with a hypersalt diet (Zweifach and Shorr 1949). Similar morphological changes were observed on the microvessels of the bulboconjunctiva of people with essential hypertension or in the presence of Itsenko-Cushing syndrome. In microvessels, the phenomena of general vasoconstriction were observed in connection with the prolongation of the contraction phase and increased sensitivity to adrenaline (R. E. Lee, Holze, 1951; Lee, 1955; Davis, Landau, 1967). The authors emphasize that morphological changes are not the cause of hypertension, but rather its consequence, i.e., secondary changes. A two-to-3-fold increase in the sensitivity of the nail bed microvessels to adrenaline in hypertensive patients was found by Davis and Landau (1958).

Increased sensitivity to norepinephrine, aigiotensin and vasopressin has occurred in rats with haemorrhagic hypotension (Gray 1971). A different pattern of changes in the response of the terminal vessels of the lungs to adrenaline was observed by D. S. Maruev (1972) in irradiated rats. In his experiments, sensitivity to adrenaline decreased and the drug at a concentration of

0.01% caused a perverse reaction of arterioles and venules: instead of constriction after radiation exposure, dilation developed.

Acetylcholine. The effect of this vasoactive drug on microvessels is less pronounced compared to epinephrine or histamine. Acetylcholine predominantly causes vasodilation, but this effect may be mild. Intravenous administration of 0.02 mg of acetylcholia to cats caused vasodilation of the soft meninges, lowering blood pressure from 110 to 40 mm Hg. (Forbes, 1929). However, the use of acetylcholia on the microvessels of the liver has proven to be ineffective (Wakim, 1942). Nor was any effect observed with the local action of acetylcholine (1:500) on the microvessels of the frog lungs. With local exposure to the microvessels of the hamster buccal sac, acetylcholine caused dilatation of arterioles and venules (Litton et al., 1967). Microionophoretic application of microdoses of acetylcholine to the arteriole wall of the hamster's buccal sac caused local dilatation of the vessel. High-speed filming showed that locally induced dilatation spread along the arteriole wall by 500 μm, which was 5 to 10 times higher than the maximum spread of local vasoconstriction from the administration of norepinephrine under the same conditions (During E. A., 1968). A few hours after exposure to ionizing radiation, a mild perverse reaction to the topical application of acetylcholine (constriction) was observed on the microvessels of the lungs of irradiated rats (D. S. Maruev, 1972). A. Krogh (1927) was unable to identify any effect of acetylcholine on blood capillaries. However, G. I. Mchedlishvili (1956) in experiments on mesenteric vessels showed that this mediator dilates capillaries, not only by changing hemodynamics as a result of dilation of the precapillary compartments, but by directly influencing the area of the capillary region. Unfortunately, these results require a critical attitude, since in the experiments a partial ligation of the arteries was performed, i.e., a serious mechanical injury was inflicted, which could not but lead to the release of vasoactive substances capable of causing the observed effect. In addition, there is reason to believe that acetylcholine itself is able to release these substances.

NERVOUS REGULATION OF BLOOD MICROVASCULAR FUNCTIONS AND THE PROBLEM OF NERVOUS TROPHISM

Innervation of the precapillary regions

Innervation of the precapillary regions is one of the most difficult sections of the whole complex problem of innervation of blood vessels. According to current ideas, sympathetic postganglionic fibers innervate the smooth muscle cells that make up the middle sheath of the arteries. Irritation of the postganglionic sympathetic fibers causes constriction of the arteries, which is why these fibers are referred to as adrenergic sympathetic fibers. After removal of the

sympathetic chain, the vasoconstrictor effect is maintained, due to "extrasympathetic" fibers that follow the course of somatomotor fibers (Folkow, 1955). There are sympathetic postganglionic fibers that cause dilatation of coronary and skeletal muscle vessels. Since the irritation effect of these fibers is inhibited by atropine, they are referred to as sympathetic cholinergic fibers (Folkow 1955; Uvnas, 1960). Sympathetic cholinergic vasodilator fibers are thought to be axons of specialized sympathetic ganglia cells. Due to the fact that these fibers are activated when the hypothalamus is stimulated, they allow their participation in emotional and stress reactions. The question of the presence of such fibers in humans has not been finally resolved. Parasympathetic dilator fibers originate from the cranial and sacral portions of the parasympathetic nervous system. They invent the vessels of the brain, tongue, salivary glands, external genitals, bladder and rectum. These fibers are parasympathetic cholinergic dilators. Many general and specific issues concerning the innervation of the great blood vessels have been covered in detail in a number of articles, review papers, and monographs (A. V. Leontovych, 1927; B. A. Dolgo-Saburov, 1936; T. A. Grigorieva, 1954; N. B. Lavrentieva et al., 1968; E. M. Krokhina, 1970; Folkow, 1955; Falck, Owman, 1965). The assumptions about the localization of ganglion cells along the course of vessels of different diameters, which determine the innervation of these vessels (A. V. Leontovych, 1927), are now refuted by direct experiments, which have shown that ganglion-blocking substances do not inhibit copstriction when preganglionic fibers are irritated (Ginzel and Kottegoda, 1953). However, there are studies indicating that nerve cells are found in the wall of a muscular-type artery (100–200 μm in diameter), and G. A. Polikarpova (1961) describes individual nerve cells located in pairs and in the wall of arterioles with a diameter of 30–50 μm. Sometimes ganglion cells are located between an artery and a vein. The author described a ganglion with a size of 95X28 μm, located in the adventitium of an artery with a diameter of 99 μm and consisting of small ganglion cells of medium size 14X8 μm. Since it was not possible to trace the course of nerve cell processes and establish the location of their endings in the vascular wall, the author does not make a final conclusion about the presence of a functional connection between nerve and muscle cells. According to existing ideas, motor innervation takes place in microvessels with a well-defined layer of smooth muscle cells. It progressively decreases with the disappearance of muscle cells on the microvessel wall (Zweifach, 1961). According to electron microscopic studies, unmyelolyzed fibers in the vessels (diameter 100–200 μm) of the fascia of the rabbit femur muscle pass at a distance of 1 μm from the muscle layer, and in the arterioles (diameter 50–20 μm) there are contacts between axons and smooth muscle cells (Rhodin, J 967). In the sphincter region, the distance between their membranes decreases to 4.5 nm. However, the author concludes that nerve fibers do not

penetrate from the adventitia into the muscular layer of the terminal vessels. When studying the innervation of the vessels of various organs and tissues, many researchers note the specificity of the innervation apparatus. For example, cholinergic nerve fibers have not been found in the vessels (diameter 30–100 μm) of human and ape skeletal muscle, while adrenergic innervation is well expressed in them (Berme and Fuxe, 1970). No parasympathetic nerve terminals were found in the vascular wall of the rat mesentery (N. B. Lavrentieva et al., 1968). There is a complete absence of adrenergic fibers in the vessels supplying the brain (Edinger et al., 1966).

Regulation of the number of open capillaries

The number of open capillaries determines the functional capacity of the capillary bed, and consequently, to a large extent, the volumetric velocity of capillary blood flow, as well as the size of the capillary filtration area, i.e. the amount of transcapillary exchange. According to very approximate estimates, the total number of capillaries in humans reaches 2 billion, and the total length of the capillaries of the great circle is 8,000 km. The area of the inner surface of the capillaries of the great circle exceeds , and the volume of blood in them is about 63 ml, i.e., approximately equal to cardiac output (A. A. Chizhevsky, 1959). Lifetime observations have established that the number of active capillaries, i.e. those in which blood flow is noted, is a very dynamic indicator. It is well known that the amount of blood flowing through the capillaries determines the nutrition and specific function of the organ, the maintenance of blood pressure at a certain level and the distribution of heat. A. Krogh spoke about this in 1999, emphasizing that the color of the skin depends on the condition of the lumen of the skin capillaries, and not on the speed of blood flow through them, while the temperature of the skin is determined solely by the speed of blood flow. When the organ is at rest, most of the capillaries are shut off from the bloodstream. It is very difficult to quantify, e.g., in percentages, this proportion, although some authors believe that it may be as high as 75% in the frog liver (Wakim 1942). In almost any organ, capillaries form such a dense network that each tissue cell is no more than 50 to 100 μm away from the capillary, and even less so in skeletal muscle. As noted above, the specific function of the organ has a morphological microcirculatory support. For example, in the muscle, from 20 to 30 capillaries branch off from the metaarteriole, and in the tissue of the gland, which does not have such an intensive metabolism, 1 to 2 capillaries originate from the metaarteriole. As cellular metabolism increases, the number of active capillaries increases and the amount of perfused blood increases. It is generally accepted that the number of active capillaries is determined by the activity of precapillary sphincters, which are controlled by the feedback principle of tissue metabolites. At rest, the muscle tone of the precapillary sphincter is high, and the permeability is comparatively low, because it is designed to meet the needs of resting tissue.

Under these conditions, a significant part of the capillaries is disconnected from the blood circulation, i.e., they are not perfused. With intensive work, intermediate metabolic products accumulate in the cells, which cause the expansion of the precapillary sphincter, in connection with which the blood flow increases and closed capillaries and sinuses are turned on. With the elimination of metabolic intermediates, the muscle tone of the sphincter increases again and the number of active capillaries decreases. It should be noted that in recent years, research has been carried out in which an attempt is made to understand the biochemical self-regulatory mechanism that ensures the opening and closing of precapillaries. At the same time, a hypothesis is put forward about the important role of metabolic autoregulation of actomyosin of smooth muscle precapillary sphincters with the help of ATP and cyclic 3',5'-AMP.25 м^{2}1927 г

The number of open capillaries is also greatly influenced by the amount of venous (post-capillary) outflow, which, by creating a certain resistance in the capillaries, can limit the flow of blood from the metaarteriole into them. In other words, the number of active capillaries under normal conditions is also determined by the ratio of arterial and venous pressure at the level of the precapillary sphincter opening. The greater the difference between them in favor of blood pressure, the greater the number of active capillaries. If there is no difference in pressure, the supply of arterial blood stops and the number of active capillaries decreases. From the above materials, an idea is created that the change in the functional capacity of the capillary bed and the area of capillary filtration occurs as a result of the action of hemodynamic factors, through which local, humoral and nervous regulation of the number of open capillaries is carried out. The capillaries themselves do not show any activity in this process. This view is accepted by most researchers, but is not universally accepted. A. Krogh (1927), for example, on the basis of his own experimental data, came to the conviction that capillaries are capable of actively changing their lumen independently of the state of hemodynamics in other parts of the microcirculatory bed. This activity, in his opinion, may be based on the contractile activity of pericytes or the process of swelling and swelling of the endothelium. Both of these assumptions remain unproven, which allows us to doubt the correctness of the conclusion about the active change in the lumen of the capillaries. However, the passive change in the lumen of the capillaries can be associated not only with the action of hemodynamic factors. The capillary wall experiences pressure from both the blood flow and the outside. The nature of this pressure is different: hydrodynamic, hydrostatic, osmotic. Hence, it can be assumed that depending on the direction of the pressure gradients, the capillary wall moves, accompanied by a change in the capillary lumen. In this case, changes in the size of the capillary lumen can primarily be associated with changes in the pericapillary space, provided that there are no hemodynamic shifts

in the pre- and post-capillary regions. Similar ideas were previously expressed by G. I. Mchedlishvili. However, in our opinion, this mechanism is able to change the size of the lumen only of already open capillaries, but is not able to open completely closed ones. It is very important to address the issue of active changes in the capillary lumen, but the histological methods most often used to address this issue do not meet the adequacy requirement, since the specimens may reflect postmortem and fixation changes. The importance of ischemia and hypoxia in the appearance of artifacts is well illustrated by the following data. Cantu (1969) perfused the capillaries of the rabbit brain at a pressure of 110 mmHg. on tracheotomized animals with artificial respiration. Experiments have shown that induced cerebral ischemia lasting up to 5 minutes does not disturb the normal conditions of perfusion and is not found in the brain (the phenomenon of the absence of capillary perfusion). With an increase in the time of complete ischemia, the area of the brain on which there was no capillary patency increased. Ischemia lasting 7.5 minutes turned off 10% of the brain surface from perfusion, and at a duration of 15 and 30 minutes — 51% and 61%, respectively.

In conclusion, it can be said that the number of open capillaries is regulated by various factors of the local environment, neurotransmitters and hormones, but the mode of their action, according to modern concepts, is indirect: through the smooth muscle cells of precapillary (and possibly postcapillary) microvessels, and ultimately through hemodynamics. These ideas do not exclude the possibility of a direct (not yet proven) influence of regulatory factors on the capillary wall with an active change in the lumen of the capillaries. Future studies will undoubtedly clarify the question of the active alteration of the lumen of the blood capillaries and the extent to which various mechanisms are involved in the passive alteration of the capillary lumen and the number of functioning capillaries.

Nervous Regulation of Blood Capillary Function and the Problem of Nervous Trophism

The question of the nervous regulation of blood microvessels, in the wall of which there are no smooth muscle cells (capillary-type microvessels), has a long history, but it has been studied only sporadically and has rarely been the subject of special research, both morphological and especially functional. The results of histological studies boil down to the recognition that capillary microvessels are occasionally accompanied by nerve elements of adrenergic and even rarer cholinergic nature, afferent and efferent. It is known that neurohistologists, both domestic and foreign, have repeatedly concluded that there are nerve endings (and, accordingly, nerve regulation) at the level of the capillary wall, but most of the evidence presented remains unconvincing of capillaries. This is understandable, given the limited possibilities of the histological method in the study of spatial relationships at the subcellular level, especially since

there were no functional equivalents of the supposed neuro-capillary connections: In general, physiological studies have not proved that capillaries have the ability to respond to nerve stimuli and neurotransmitters. The effects that were sometimes detected (changes in the size of the lumen, capillary filtration, the appearance of tortuosity, etc.) were easily explained by hemodynamic shifts in the microcirculatory bed due to the reactions of microvessels with a muscular membrane. However, researchers have long had, but have not used, a fact that directly indicates the reality of the existence of regulation of the state of capillary microvessels by the nervous system. This fact was represented by pathophysiology. Its essence lies in the fact that when the innervation of organs and tissues is disturbed, vascular permeability changes significantly. Indeed, the main role of the capillary wall is transport (organization of transcapillary exchange) and protective (barrier) function. Both of these functions are now well known to rely on the same structural equivalents, and vascular permeability is a common characteristic. Therefore, it is clear that a change in vascular permeability presupposes the existence of ultrastructural changes, primarily in the endothelium, which directly indicates the dependence of the structure and function of capillary microvessels on nervous influences. This relationship was tested using the electron microscopic method. Two experimental models were used: unilateral or bilateral vagus neuritis in rabbits and skeletal muscle denervation in rats. In the first case, subepineural injection of 0.05 ml of resinated turpentine was performed (the nerve was exposed in the neck) and after 1-3-5 hours. Pieces of the lungs and myocardium (apex) were taken for electron microscopic examination. 30 seconds or 1 hour before tissue collection, the animals were injected intravenously with colloidal charcoal (purified mascara 1 ml/kg) and iron oxide saccharate (200 mg/kg). Pieces of the calf muscle were taken from rats after 20 days. after cutting the motor nerve, the central and peripheral ends of which were immediately sewn together. Colloidal carbon (0.1 ml/100 g body weight) and iron oxide saccharate (50 mg/100 g) were used as indicators of vascular permeability, the circulation time of which was 20 and 2 minutes, respectively. The control was falsely operated animals that were injected intravenously with indicators at the same doses. In the first series of experiments, changes were found in the microvessels of the lungs and heart, which were expressed in an increase in the number of folds and microvilli on the surface of the endothelium, increased vacuolization and microbubble formation, and the appearance of local expansions of the subendothelial space. Microhemocirculatory disorders were also noted: aggregation of erythrocytes and platelets, increased adhesion of blood cells to the endothelium, accumulation of granulocytes in the vessels. Individual changes have been made In bilateral neuritis, they developed more rapidly, especially interstitial edema. Based on the data on the increase in the activity of the endothelial

surface, it can be assumed that there is also a change (increase) in the diffusion permeability of the membranes of endothelial cells. This may be one of the reasons for the increase in the number of light-colored edematous cells in the endothelium, which was observed in the microvessels of both organs. The study of denervated muscle microvessels in rats revealed significant ultrastructural changes in the endothelium at both follow-up periods. The most important here was the discovery of the channels connecting the lumen to the basement membrane. This fact suggests that filtration is directed into the tissue rather than out of the tissue, indicating significant shifts in the gradients that determine the direction of filtration through the venous vessel wall. The formation of interendothelial clefts is explained by the divergence of cells as a result of their contraction. This reduction is thought to be due to the function of cytoplasmic microfibrils. However, we cannot unequivocally link the formation of clefts with cell contraction due to microfibrillar elements. It must be recognized that endothelial cell contraction can be carried out by a variety of mechanisms. Further, the characteristic features of the interendothelial fissures in this case are the preservation of the zones of tight junctions and the presence of finger-like protrusions in the fissure and along the perimeter of the cells. These data, as well as the results of the study of serial sections, allow us to conclude that the gaps are formed not as a result of a simple divergence of adjacent cells, but as a result of local lacing of one of them in the area of thinning or perforation of thinned areas during the fusion of vesicular structures. In some cases, the clefts are both interendothelial and transendothelial. The appearance of thinned peripheral areas can be attributed to cell contraction, and perforation can be explained by increased microvesiculation and vacuolization. In these studies, the authors encountered the fact of the formation of microbubbles in the area of contact surfaces. This can result in the rupture of the thinned walls or the complete delamination of the contacting cells with the formation of interendothelial clefts in both cases. In microvessels with thinned endothelium (capillaries), increased microvesiculation, vacuolation, and deep indentations of the endothelial surface caused the appearance of transendothelial channels. These channels were also located on the periphery of the cells, but did not affect intercellular contacts. Thus, both acute disorders of the nervous regulation of organs (vagus neuritis) and longer ones (denervation) lead primarily to changes in the activity of the endothelial surface and related processes, ultimately leading to the formation of interendothelial clefts and transendothelial canals. Single electron microscopic studies available in the literature also indicate a rapid and profound response of capillary microvessels to changes in the nervous regulation of organs (rialaris, 1971; Takahashi, E. A., 1966). The very idea of the possibility of regulating capillary blood flow by means of the mechanism of swelling-swelling of endothelial cells, as is known, was discussed by Krogh

(1929). Electron microscopic data and the results of intravital studies of microcirculation indicate that this phenomenon does occur, but its regulatory role in relation to capillary blood flow has not yet been proven. However, swelling (edema) of the endothelium may play a leading role in the mechanisms of disorders of capillary blood flow under conditions of pathology, for example, in the development of the phenomenon of "re-restoration of blood flow" after a short-term interruption of blood circulation in the organ (Ames e. a., 1968). It is clear, therefore, that the swelling of endothelial cells is pathological rather than physiological. Let us assume that the "movements" of the capillary wall are expressed in phenomena other than swelling and swelling, and that these supposed "movements" are regulated by the terminal-pericyte system on the basis of neuropericytic synapses. Based on the supposed universality of this regulatory mechanism and its functional importance, it is possible to draw a practical conclusion about the frequency of detection of such synapses, especially since there can be 1—3 of them per pericyte with relatively large endings (judging by the illustrations, from 1 to 5 μm). It is clear that these synapses cannot be missed when viewing slices even at small electro-optical magnifications and should occur quite frequently.

It is known that under the influence of neurotransmitters and during electrical stimulation of nerves (afferent and efferent), free vasoactive substances appear in tissues: prostaglandins (Ramwel e.a., 1965), histamine (Arabarche, Barsoum, 1939; Lambert, Rosenthal, 1940; Kwiatkowski, 1943; Anrep e. a., 1944, et al.), ATP (Burnstock, 1972), and possibly others. In general, the analysis of the literature data shows that there are close structural and functional connections between vasoactive substances and the peripheral nervous system, and functional connections are built on the principle of reverse (mainly negative) connections. Of the connective tissue cells that can mediate nerve-regulatory effects on blood vessels, mast cells with α-adrenic receptors and cholinesterase activity should be mentioned first of all (Oliveira and Rothschild, 1968; Salpeter, 1969). It has been shown that in case of experimental disturbance of the innervation of organs (denervation of skeletal muscle and heart), the content of histamine in them changes, and its release and release into the outflowing blood occurs, as well as the number of mast cells (in the myocardium) decreases (II. V. Archakov, Y. S. Zhosanov, 1971). The study of the innervation of connective tissue cells revealed close spatial relationships between nerve endings and mast cells (Diculescu E. A., 1969). Of course, when talking about the innervation of mast cells, it is necessary to take into account their mobility and the possibility of relatively rapid changes in their number in tissues in various states of the latter. Of great interest are studies showing that electrical stimulation of the celiac nerve leads to degranulation of mast cells in the mesentery (Oliveira and Rothschild, 1968). Based on these data, it can be assumed that mast

cells (it is quite possible that they are not the only ones), mediating the nervous regulation of microvessels, act as biological transformers and amplifiers of nervous influences on the vascular wall, especially in pathological conditions.

In general, it follows from the above data that the nervous regulation of capillary microvessels is carried out not according to the "telephone" principle, but according to the principle of "regulatory situations", i.e., on the basis of specific ratios of neurotransmitters and vasoactive substances. Functionally related, they all act not individually, but in a complex, and each of them, depending on the general regulatory situation, can exhibit different properties in relation to the capillary wall. It is also necessary to take into account that vasoactive substances are factors of the local environment, the most important elements of the system of local self-regulation. Consequently, it is through them that the central regulatory mechanisms are connected with the system of local self-regulation. And it is not known what is more important in this or that case: the direct effect of neurotransmitters on the capillary wall or indirectly, through vasoactive substances. However, in those places where the nerve endings are located in the immediate vicinity of the endothelium or pericytes (variants A and B in the diagram under discussion), i.e., where direct and rapid nervous regulation of the microvessel can be carried out, this question is solved simply and unambiguously. How can the capillary wall react to direct or indirect nerve impulses, i.e., which property or function of the capillary wall should be regulated in the first place? We answered this question at the very beginning of this section: nervous regulation (and any other) here should first of all be aimed at regulating the basic property of the capillary wall, namely its selective permeability, which determines the state of the barrier and transport function of the capillary wall. On the basis of functional-morphological and pathomorphological analysis, it was shown that the endothelial surface and the absorption and transport mechanisms associated with its activity have the greatest structural and functional mobility, while intercellular contacts are more conservative and, accordingly, interendothelial transport, at least in the presence of "tight contacts", is less regulated. Nervous regulation of the capillary wall is mainly the regulation of the functional state of the surface of endothelial cells. It is also known that adrenaline increases the absorption activity of endothelial cells in the capillaries of individual organs. It should be recognized that more extensive research is needed on the effects of neurotransmitters and vasoactive substances on endothelial surface activity and capillary wall health. Thus, the nervous regulation of the capillary-venular part of the microcirculation is carried out through direct, predominantly synaptic, connections of the nervous system with the wall of capillary microvessels, as well as by mediation through cells that secrete vasoactive substances. Direct and indirect pathways of nervous regulation can play

different roles in changing normal conditions and in pathology. In this case, the object of nervous regulation is the substrate through which the blood-tissue metabolism takes place, i.e., the actual trophism of the tissues is carried out. Thus, a new link in the mechanism of neurotrophic regulation of organs and tissues is revealed, namely the capillary-venular part of the microcirculation system. The regulation and trophic influence of nerves on tissues through the circulatory system is mediated not only by rough regulation of blood flow to the organ and its parts (I. P. Pavlov), but also by subtle regulation of the trophism itself through a change in the state of the wall of microvessels.

METHODS OF STUDYING MICROCIRCULATION

Methods for studying microcirculation include, in addition to traditional histological examination, electron microscope examination, as well as intravital microscopic diagnostics of blood flow disorders (study of the capillaries of the nail fold, conjunctiva, gums, mucous membranes). In ophthalmology, fundus vascular microscopy is widely used, which makes it possible to assess not only the appearance, but also the permeability of the vessels when injecting luminescent indicators into the blood. For this purpose, the subcutaneous Landis test is also used to determine the permeability of capillaries by the amount of filtration of fluid and protein from capillary blood under conditions of increased hydrostatic pressure. The value of interstitial pressure can serve as an indicator of the state of water balance in tissues. Radionuclide methods are increasingly used to summarize tissue blood flow, blood extraction, and clearance of various substances. Viscometers are being introduced into clinical practice to study the aggregate state of blood at different shear rates. In biomedical experimental research, the methodological possibilities for studying microcirculation are more extensive and informative. Almost all the most important parameters that reflect the functions of the microcirculation system are available for quantitative analysis.

Electron microscopic studies of perivascular transport are just beginning. There are no special methods, no methodology has been developed. However, ideas are already being formed, trends and possible paths of development are outlined.

The permeability of lymphatic vessels was studied only in the tissue-lymph direction. At the level of light microscopy, there are isolated studies of permeability in the opposite direction. For example, Zweifach (1972) micropipetted the small lymphatic vessels of the mesentery with Evans' blue dye in saline solution or with serum albumin. In the first case, he observed a diffuse exit of the dye from the lymphatic capillaries into the tissue, in the second, a discrete one, so that colored dots were formed near the wall, as if the exit was carried out through channels separated

from each other. It is clear that the micromolecular dye in the first case could have escaped by diffusion through endothelial cells, and in the second case (in connection with the protein) only through the intercellular clefts. These data also indicate the possibility of the existence of bilateral exchange at the level of lymphatic capillaries, but this issue has not yet been fully studied.

The study of lymphatic capillaries under biomicroscopy using a combination of the "dark field" technique and the use of fluorescence technique in blue light is noteworthy (Hauck, 1972). This method made it possible to identify some topographic features of lymphatic capillaries and blood microvessels. The initial lymphatic vessels, according to this author, are gaps in the tissues. Lymphatic microvessels usually accompany small veins (the venular part of the capillaries, venules and small collector veins), i.e. those microvessels where the penetration of large molecules is most intensive. The author observed that connective tissue fibers represent pathways for the advancement of extravascular fluid. They are the link between the blood capillaries and the lymphatic vessels in lymphatic drainage.

Unfortunately, there are very few biomicroscopic studies devoted to the study of the structure and function of lymphatic capillaries. At the same time, only a comparison of the ultrastructural and biomicroscopic characteristics of these vessels will make it possible to reveal the mechanism of the drainage function of lymphatic capillaries.

CHANGES IN MICROCIRCULATION IN DISEASES

Local or generalized microcirculation disorders occur in almost all diseases. In accordance with the functional properties of the microcirculation system, these disorders are manifested by a complex of different syndromes. For example, in shock of different etiologies, the phenomena of tissue hypoperfusion, i.e. insufficiency of capillary blood circulation, and the aggregation of erythrocytes, i.e. the formation of their conglomerates of different sizes and densities, acquire leading pathogenetic significance. Impaired permeability of the microvascular walls to fluid and protein, as well as leukocyte infiltration in the focus of acute inflammation, is the result of a specific microcirculation response. in conditions of a complex balance of mediators: histamine, serotonin, complement system, arachidonic acid derivatives, reactive oxygen species and others.

Persistent contraction of resistive microvessels, arterioles, and structural transformations of their walls serve as an effector mechanism for the development of hypertension syndrome. At the level of microcirculation and with its direct involvement, such severe conditions as disseminated intravascular coagulation syndrome develop. In the development of pathological conditions, syndromes of microcirculatory disorders are often combined in various combinations

and manifest themselves with different intensity. The state of the structural and functional units of the microcirculatory bed is used to judge the working loads and the state of the microcirculation system as a whole. Changes in the microcirculation system occur in many diseases. In turn, microcirculation disorders can cause pathology and processes in organs. Determination of the level of microcirculation is used in the treatment of burn disease, coronary heart disease, monitoring the condition of patients during prolonged and traumatic surgical interventions.

The question of changes in capillary circulation and the role of these changes in the general pathology of blood circulation is important. Usually, microcirculation disorders in the general pathological sense are divided into intravascular, vascular, and extravascular-perivascular. Intravascular disorders are disorders of the rheological properties of blood associated with changes in the suspension stability of blood elements and its viscosity, with blood coagulation disorders and impaired perfusion through the microcirculation system. Vascular disorders are caused by changes in the diameter, shape, number of functioning vessels, changes in the properties of their endothelium and basement membrane. Extravascular disorders are a reaction of the connective tissue, mast cells, etc., surrounding microvessels, to pathological irritation, lymphatic circulation disorders, involvement of the microvasculature bed in the neurodystrophic tissue process. It should be emphasized that these microcirculation disorders are closely interrelated and interdependent and occur, as a rule, in their various combinations.

Signs of normal and altered blood condition

№	Normal Blood Circulation	Sludge state
1.	Individual red blood cells, platelets, and white blood cells	Each erythrocyte, leukocyte or platelet, or a collection of these cells, combines with each other to form aggregates
2.	The surface of the cells is natural and when they come into contact in the bloodstream, they do not stick to each other	Cells, especially erythrocytes, have a damaged surface and stick to each other at any contact in the bloodstream or removed blood. Leukocytes adhere to the walls (endothelial cells) of microvessels.
3	The cells do not adhere to the endothelial walls of the microvessels and sinusoids of the liver.	Erythrocytes can adhere to the cells of the sinusoid wall and be phagocytosed by the latter. A clear boundary between the cell surface and their plasma is lost.

4	Erythrocytes and other cells have an unaltered membrane and a clear demarcation of their membrane surface from the cell's plasma	The nature of the laminar current changes due to the thickening of each layer.
5	Each blood cell represents a single element, and the blood flow is laminar. Each layer of the blood stream has the thickness of one red blood cell.	Then there are vortex movements, and finally a slow current and blockage of the lumen of the microvessels are established.
6.	The magnitude of blood flow at the appropriate magnification of the microscope in the microvessels optically does not make it possible to distinguish individual cellular elements. They merge into one homogeneous red stream with a lighter central part (axial flow)	The formation of aggregates reduces the magnitude of blood flow, which further increases the size of aggregates; The homogeneity of the flow disappears and the aggregates become more and more clearly distinguishable, and later their precipitation occurs.
7	The viscosity of blood plasma is normal (not too watery and not too viscous), which is explained by the optimal number and proportions of different fractions of blood proteins.	Due to the decrease in the velocity of blood flow, the liquid part of the plasma containing the colloid passes mainly through the walls of the venules into the tissues and the blood becomes more viscous.
8	The walls of the blood vessels are adequately nourished and have a normal shape The permeability of the microvascular walls is normal, so there is no large loss of plasma fluid, and therefore no hemoconcentration or tissue edema	The walls of the blood vessels do not receive adequate nutrition and begin to lose their normal shape The walls of the venules become increasingly permeable to the liquid parts of the plasma, resulting in an increase in blood concentration.
9	The blood volume is adequate and corresponds to the different states of tissue	

10	metabolism. In any physiological state of tissues, the distances for diffusion and the distances between microvessels ensure the constant movement of tissue fluids, metabolites, catabolites and gases.	The number of erythrocytes decreases due to their blockage of small vessels, as well as due to increased phagocytosis of these cells in the liver, spleen and bone marrow. All this leads to a partial reduction (narrowing) of the lumen of these vessels and an increase in the distances for the diffusion of various substances.

Microcirculation and smoking

There is evidence in the literature that shows the role of smoking among other risk factors (RFs) for CHD. In studies conducted in Andijan, it was found that among smokers, especially those of Russian nationality, there is a higher incidence of CHD than in the general population: the coefficient of determination – the "contribution" of the factor of smoking and susceptibility to CHD was 10.5%. Among Uzbek male smokers, there is also an increased incidence of coronary artery disease, which, however, is less pronounced, while the estimate of the coefficient of determination (1%) was unreliable. This indicates ethnic differences in the responses of the body systems responsible for the development of CHD to the smoking factor.

IN THE literature available to us, we found only a few data on the influence of the habit of smoking on the state of MCB in CHD. Thus, the data of Dmitrieva V.I. showed that smoking causes an increase in the activity of the blood coagulation system and inhibition of enzymatic and non-enzymatic fibrinolysis both in patients with stable angina pectoris and in patients with stable angina pectoris. persons without clinical manifestations of coronary artery disease. These adverse changes are more pronounced in women than in men. Shevtsov V.E., having studied the state of the MC in patients with CHD at a young age and the effect of physical activity and tobacco smoking on it, revealed in healthy patients narrowing of the venules and dilation of the arterioles, and in patients with CHD - narrowing of the arterioles and venules. At the same time, there is an increase in the aggregation of blood elements.

Thus, these data suggest that there is a definite relationship between "the state of MCB and smoking as a risk factor for coronary artery disease.

Microcirculation and Alcohol consumption

One of the possible factors predisposing to the development of CHD is the consumption of alcoholic beverages. Numerous works are devoted to the study of the effect of alcohol on the state of various organs in this pathology. Works devoted to the study of the role of alcohol in microcirculatory disorders, according to the available literature, are found in isolated cases.

The authors who studied this issue found peculiar changes in the blood supply to the organs at the capillary level. Thus, the most pronounced deviations in the MCB were detected by conjunctival biomicroscopy in patients with alcoholism. In most cases, they had peculiar arteriolo-venular "anastamoses" (when the capillaries were empty), the venular segment of which looks like a cone-shaped corkscrew.

It follows from the literature that the problem of the relationship between the use of alcoholic beverages and the state of MCB in CHD has not yet been sufficiently studied and requires further solution.

Microcirculation and hyperlipidemia

At present, questions about the role and place of MC disorders in CVD, in particular in atherosclerosis, are becoming relevant. Traditionally, there is a point of view that changes in the terminal vascular bed occur after the atherosclerotic process affects the great vessels or develop in parallel.

Hyperlipidemia is known to significantly affect the microvessels, altering capillary blood flow, making it difficult for oxygen to pass from the blood to the tissues, causing microangiopathy. Therefore, hyperlipidemia, in addition to being one of the factors of atherogenesis, directly affects hemodynamics and oxygen transport to tissues, and is also involved in the pathogenesis of coronary artery disease. This pathway should be considered non-atherogenic.

It is known that hyperlipidemia in patients with CHD is accompanied by significant shifts in the microcirculation system, changing capillary blood flow, impeding the transfer of oxygen from the blood to the tissues, causing microangiopathy. Therefore, hyperlipidemia, in addition to being one of the factors of atherogenesis, directly affects the hemodynamics and transport of oxygen to tissues, and participates in the pathogenesis of coronary artery disease. This pathway should be considered non-atherogenic. For example, the majority of patients with CHD in various vascular regions have microcirculation disorders characterized by changes in tissue blood flow, capillary permeability, microhemorheology, microthrombosis, and microvascular architectonics. In the chronic course of coronary artery disease, there are regular disorders in the microcirculation system, which cover both the process of hemodynamics itself and the structure of the elements of the terminal vascular bed. These changes, in different combinations with each other, are important in aggravating circulatory disorders. Many researchers have proven that the initial changes in microcirculation are manifested by functional disorders, then, as the disease worsens, capillaries, arterioles and venules change, and platelet aggregation is observed. This is accompanied by a slowdown in blood flow, mainly in the venules, which in turn increases blood

viscosity and further aggravates microhemodynamics. Of the perivascular changes, hemosiderosis is observed.

Impaired microcirculation is more pronounced when emotionally painful stress is combined with experimental HCH. Morphofunctional changes in erythrocytes in experimental HCHS caused by an increase in the content of cholesterol in membranes lead to increased erythrophageal function of the spleen, hemolytic anemia, and impaired rheological properties of the blood, which is important for understanding the pathogenesis of atherosclerosis.

According to many authors, along with obstruction of the microcirculatory bed, platelets cause a number of humoral shifts due to the release of biologically active substances from them. These substances, by activating or inhibiting blood coagulation and thrombosis, affect a number of organs and systems. The most important change is the diameter of the lumen of the vessels and their permeability.

Spastic-atonic states of microvessels with obliteration of a large number of capillaries in the limbal and perilimbal areas of the microaneurysm are observed. The degree of these impairments correlates with the severity of the disease.

Microcirculation and arterial hypertension

A long-term increase in blood pressure causes tortuosity, the formation of loops in the true capillaries, especially in the collecting venules, at the same time there is a narrowing of the terminal arterioles, as well as an increase in the sensitivity of smooth muscles and microvessels to adrenaline. At the same time, there is a slowdown in blood flow. These observations have been researched and confirmed by many authors over the years. For example, during the study of the ultrastructure and permeability of the aortic endothelium for microparticles, peroxdase and feritin with a persistent increase in pressure of renal origin, the expansion of the subendothelial space, the appearance of granular material, fibrin, leukocytes and lymphocytes in it was noted. An increased number of microvesicles was found in the cytoplasm of endothelial cells. Based on this, it was concluded that in the early stages of hypertension there is only activation of normal transport mechanisms, in particular microvesicular transport through the endothelium [22,23,27].

Also, some authors have proven that long-term alternate use of vasoconstrictors and vasodilators leads to necrosis of smooth muscle cells and an increase in endothelial permeability to plasma proteins, but not to colloidal iron. Studies show that arterial hypertension in the early stages of development leads to an increase in endothelial permeability due to the strengthening of the physiological transport mechanism, and then pathological transport pathways are detected, the appearance of which is due to destructive processes in the endothelium. The destruction of

the endothelium is facilitated by the state of vasodilation, which is associated with the destruction or "weakening" of smooth muscle elements.

Under the influence of psycho-emotional stress in patients with borderline arterial hypertension, spastic-atonic reactions of microvessels, a slowdown in the velocity of capillary blood flow with a tendency to stasis and the formation of erythrocyte aggregants, a decrease in oxygenation of tissues, which persist even after stress, were noted. According to the observations of some authors, in young patients in the 1st and PA stages of hypertension (AH), there is a narrowing of the arterioles and dilation of the venules, leading to a decrease in the arteriovenular ratio, as well as to an increase in tortuosity and irregularity of the vessels, which, in their opinion, can serve as an additional diagnostic test. Other researchers found a moderate slowing of blood flow in the biomicroscopy microvessels and the appearance of coarse-grained aggregation of erythrocytes in the venules, moderate narrowing of the arterioles and dilation of the venules. This degree of impairment is characteristic of the initial stage of hypertension and atherosclerosis. In patients with stage II hypertension with severe atherosclerosis, microcirculatory disorders of stage II are found, which is characterized by: diffuse coarse-grained aggregation of erythrocytes and a pronounced slowdown of blood flow in venules and capillaries, significant spasm of arterioles, and a decrease in the number of functioning capillaries [27,29].

According to N.N. Kryukov, microcirculation disorders are detected as early as stage 1 of AH. At the same time, the author observed a decrease in the number of functioning capillaries, stasis in single venules, irregularity of the caliber of arteries and venules, tortuosity, perivascular edema, early reaction of the capillary, venular and perivascular links. During the period of stabilization of the increase in blood pressure, arterioles were also involved in the process.

Some authors confirm that in the majority of patients there is a correlation between the nature and severity of changes in the conjunctival microvessels and the stage of AH. A study of a group of healthy individuals and a group of patients with hypertension aged 31-75 years revealed that microaneurysms, ischemic zones, and widespread aggregation of erythrocytes in the microvessels of the bulbar conjunctiva were observed in the group of patients 3-5 times more often than in the control group. Microhemorrhages along the conjunctival microvessels were not detected in the control group, and in hypertension they were found in 11 out of 25 patients. In the same studies, there was a greater frequency of these changes in the vessels of the bulbar conjunctiva in stages A and B of AH compared to stage 1.

In atherosclerosis and hypertension, the permeability of blood vessels to plasma proteins decreases, the transfer of oxygen from the blood to the tissues is also impeded, and the amount of oxygen utilization by tissues decreases.

One of the complications of hypertension is vascular thrombosis, in the development of which changes in the properties of the vascular wall and platelets are of great importance.

Thus, in arterial hypertension, the functional nature of disorders at the initial stage of the disease is replaced by organic changes and progression of the process [32,33,36,37].

Microcirculation and atherosclerosis

Changes in microcirculation in atherosclerosis resemble those in hypertension, especially since these diseases are often combined. In 42% of cases, there is an increase in vascular fragility. According to many authors, disorders of microcirculation and rheological properties of blood were observed in patients with atherosclerosis during the progression of the disease. Microcirculation disorders correlated with the clinical picture of the disease, the dynamics of the coagulogram, as well as with disturbances in the function of external and internal respiration, shifts in acid-base balance and lipoprotein profile. The aggregation of erythrocytes and changes in blood flow were reversible, sometimes the normalization of microcirculation preceded the improvement of the patient's condition.

In the course of atherosclerosis, initial changes in the vascular wall, characterized by the proliferation of smooth muscle cells and cholesterol deposition, and later changes, including the possible formation of a parietal thrombus, can be distinguished. Comprehensive studies of the functional and morphological state of the microcirculation of the anterior part of the eye in patients with atherosclerosis have established the following: already at the initial stage of atherosclerosis, there are significant disturbances in the vessels of the limbus and conjunctiva. As the severity of general atherosclerosis increases, these disorders progress. The degree of severity of functional disorders of microcirculation correlates with the blood supply to the eye and destructive changes in the iris. In atheroscleroma, the meanderic tortuosity of the vessels increases, the ratio of arterioles and venules decreases, and venular succulations appear. With progression, disorders of microcirculation and rheological properties of the blood were observed. According to other authors, the signs of microcirculation disorders are most clearly manifested in the capacitive part of the terminal vascular bed. Clinical severe atherosclerosis is characterized by an increase in capillary permeability to fluid and protein. Aggregation, stratification of blood flow in the microcirculation in atherosclerosis is reversible. The Knisel phenomenon in acidosis, hypercapnia, hypocapnia, hypoxia was changed in the direction of increase or decrease, being

one of the objective tests for detecting the prethrombotic state and for monitoring the effectiveness of etio-pathogenetic treatment of this disease [25,28,34].

Clinical and experimental studies have established the important role of dyslipoproteinemia as one of the leading risk factors in the development of atherosclerosis.

Hyperlipidemia is known to significantly affect the microvessels, altering capillary blood flow, making it difficult for oxygen to pass from the blood to the tissues, causing microangiopathy. Therefore, hyperlipidemia, in addition to being one of the factors of atherogenesis, directly affects the hemodynamics and transport of cyalogenium to tissues, and is also involved in the pathogenesis of coronary artery disease. This pathway should be considered non-atherogenic.

Studies conducted in this direction have shown that among healthy individuals with high cholesterol, 27% had atherosclerotic angiopathy of the conjunctiva. Compared to the normal group, the following were significantly more frequent: lumen irregularity, moderate narrowing of arterioles, increased intravascular aggregation of erythrocytes, and perivascular infiltration. The influence of hypercholesterolemia on intravascular aggregation was also noted by a number of other authors, who in the course of their studies came to the conclusion that the main role in the violation of intravasal status is played by plasma, platelet and erythrocyte coagulation factors, an increase in the activity of the Kallekrein-kinin system, and shifts in the lipid spectrum of the blood. In patients with coronary artery disease with low coronary reserve, perivascular edema and microhemorrhage, which is a sign of impaired permeability and fragility of microvessels, were determined.

In the works of other authors, it was shown that intravascular aggregation of erythrocytes (EA) occurs in 75% of the examined. In the group of patients with cardialgia with hyperlipidemia, who were considered to be at risk of developing coronary artery disease, 50% of cases had grade 1 EA, and the remaining 50% of the examined patients had grade 11 EA. It was concluded that the constant aggregations in the postcapillary venules with intermittent aggregation in the large and capillary venules found in 50% of the examined in this group indicate that hyperlipidemia is a powerful factor influencing microcirculation. Based on these data, the following conclusion was made: the presence of hyperlipidemia in patients with CHD contributes to a more pronounced decrease in tissue blood flow associated with intravascular changes at the level of microvessels. In patients with coronary artery disease and cardialgia with hyperlipidemia, microvascular reactivity indices indicate a decrease in the ability to respond to vasoconstrictor and vasodilatory influences. Changes in microcirculation in patients with CHD in hyperlipidemia are aggravated.

Microcirculation disorders are more pronounced when emotionally painful stress is combined with experimental hypercholesterolemia. Morphofunctional changes in erythrocytes in experimental hypercholesterolemia caused by an increase in cholesterol content in membranes lead to increased erythrophageal function of the spleen, hemolytic anemia, and impaired rheological properties of the blood, which is important for understanding the pathogenesis of atherosclerosis [25,28,34].

Microcirculation and diabetic angiopathy

Impaired microcirculation in diabetes (angiopathy) is no longer in doubt and is a fairly common symptom of this disease. One of the most pronounced clinical manifestations of diabetic angiopathies is diabetic retinopathy. This form of microcirculation changes is especially clearly expressed in young patients without any pronounced manifestations of renal pathology. There are five stages of this disease:

1) microaneurysms detected visually and by fluorography
2) small exudates in the posterior chamber of the eye with microaneurysms
3) large hemorrhages and exudates covering the fundus of the eye
4) new vascularization and proliferating retinitis
5) retinal detachment and punctate hemorrhages

It has been discovered that diabetic microangiopathy is based on damage to the basement membrane of microvessels with concomitant changes in the endothelium.

The process culminates in sclerosis and hyalinosis of the vessel wall. The lesion is generalized. It is important to note that morphological changes in microvessels are ahead of clinical forms of the disease. Biopsy can be recommended as a method of early diagnosis of this form of angiopathy. Some foreign authors have studied the condition of glomerular capillaries in diabetic nephropathy. They found that in the initial stage, the basement membranes are uniformly thickened, later loosened, and contain granules and inclusions that penetrate them from endothelial cells. Thickened basement membranes, according to their data, consist mainly of neutral or slightly acidic mucopolysaccharides.

Microcirculation and CHD

It is now generally accepted that changes in microcirculation play an important role in the pathogenesis of CHD. In the majority of patients with coronary artery disease, microcirculation disorders are detected in various vessels, characterized by changes in tissue blood flow, capillary permeability, microhemorheology, microthrombosis, and microvascular architectonics.

Dynamic study of microcirculation disorders in CHD can be one of the objective tests for detecting a prethrombotic state and for monitoring the effectiveness of etiopathogenetic treatment of this disease.

On the basis of long-term observation and research, the syndrome of capillary insufficiency was identified, the main pathophysiological consequence of which is hypoxia, which occurs as a result of organic or functional insufficiency of transcapillary metabolism. Subsequent numerous studies have shown the importance of this phenomenon in the pathogenesis of atherosclerosis and coronary artery disease.

It is difficult to determine the specific weight of CHD with predominant damage to microvessels in the overall structure of CHD, since it requires special methodological approaches, which are almost impossible to apply on a mass scale. In patients with chronic coronary artery disease, there are regular disorders in the microcirculation system, which cover both the hemodynamic process itself and the structure of the elements of the terminal vascular bed. These changes, in different combinations with each other, are given an important role in aggravating the circulatory disorders that occur in this disease. It has been established that initially changes in microcirculation are manifested by functional disorders, then, as the disease worsens, capillaries, arterioles and venules change, platelet aggregation (sludge phenomenon) is observed.

Spastic-atonic conditions of microvessels with obliteration of a large number of capillaries in the limbal and perilimbal areas of the microaneurysm are observed. Stasis of blood flow in venules and capillaries occurs in 68.3% of cases, in all links of microcirculation - 19.5% of cases. Based on these data, it can be concluded that microcirculatory disorders precede the clinical manifestations of coronary artery disease, are detected at the onset of the disease, increase with its progression, and may play an important role in the development of complications.

Studies of the state of microcirculation in dynamics in patients with post-infarction cardiosclerosis have shown a decrease in the degree of microcirculation disorders - a decrease in perivascular changes, sludge, an increase in devascularization due to the specific density of capillaries, an expansion of the diameter of arterioles in comparison with those in patients with acute myocardial infarction. However, insufficient restoration of the spatial organization of microcirculation necessitates mandatory dispensary observation of patients with post-infarction cardiosclerosis with the inclusion of the method of biomyocroscopy of bulboconjunctival microcirculation in the examination complex.

From the above literature data, it can be seen that a large number of studies are devoted to the study of microcirculation in cardiovascular pathology, which indicates that microcirculation

in CHD undergoes significant changes, and taking these changes into account undoubtedly improves diagnostics and helps to predict CHD more accurately.

The study of the state of microcirculation in population studies makes it possible to determine the features of microcirculatory changes in the population depending on age, region and other factors, to clarify the role of these changes in various, especially preclinical stages of CHD, which is especially necessary for preventive measures in CHD [20,21,26].

CHD and familial predisposition

It is known that many factors lead to the development of coronary artery disease, and hereditary factors play a significant role. Genetically determined risk factors for CHD include: sex of the proband, type, physique, personality traits, certain structure of coronary vessels, elevated level of total cholesterol (CH) in blood serum, low- and very low-density lipoproteins (LDL and VLDL), low concentration of high-density lipoproteins (HDL), low activity of LDL receptors, that is, disorders that can be combined into a group of lipid metabolism disorders, disorders in the coagulation blood system (tendency to increased blood clotting, which creates prerequisites for thrombosis), arterial hypertension, diabetes mellitus. Numerous clinical and twin examinations have provided insight into the nature of hereditary mechanisms that predispose to the development of CVDs.

A family case of CHD is a well-known factor. The role of genetic factors in the occurrence of a number of risk factors for CHD, which are involved in one degree or another of atherogenesis, has been proven. Familial hypercholesterolemia has been recognized as a hereditary disease. Studying the issues of hypercholesterolemia, the following conclusions were drawn: first, humans have at least two different types of lipoprotein receptors in the liver – one for chylomicrons, the other for LDL; secondly, the genetic receptor defect in large FHCs affects only LDL receptors, and heterozygotes have a lack of receptors; Thirdly, a decrease in the number of receptors and LDL in patients with FH leads not only to a violation of LDL catabolism, preventing a further increase in LDL levels in the blood, but also increases the danger of accumulation of LDL by peripheral cells and macrophages and leads to the progression of atherosclerosis [30,31,35].

Clinical and genetic studies of the hereditary burden of CHD and AH in different genetic structures in heritage groups indicate the diversity of the contribution of genetic factors to the determination of certain biochemical and functional parameters. This is due to the fact that CHD and hypertension are multifactorial diseases caused by a complex interaction of genetic and environmental factors.

On the basis of a genetic and epidemiological study, it was established that the data of the family history questionnaire (death from a heart attack of the father or mother, death of the father from a stroke, the presence of hypertension, stroke, diabetes in the mother). In men of the Baku population aged 20-54 years, it is more common in persons suffering from CHD compared to persons without this disease. It is believed that the following signs are the most informative in terms of assessing the likelihood of developing coronary artery disease; age, increased levels of Chronic Hepatit C and Chronic Hepatit, LDLC concentration, stroke in the mother, death from stroke or heart attack of the parents.

It is believed that an increase or decrease in blood pressure compared to the norm is the result of the interaction of genetic and environmental factors. One of the factors most closely related to BP levels is body weight, the variability of which is also determined by the interaction of heredity and environment.

There is reason to believe that the familial predisposition to CHD is realized through the accumulation of known RFs in these families; It is quite natural that family members, in addition to genetic similarity, often lead the same lifestyle in terms of nutrition, physical activity, smoking, etc. The main pathophysiological phenomenon in CHD ischemia appears to be the result of a combination of internal and external factors. A number of authors have found a strong relationship between the severity of atheroxlerosis and the concentration of apoliproteins (Apo, A, B). In serum, atherosclerotic changes in the coronary arteries are possible, and CHD may occur due to genetically determined disorders of certain enzymes.

When studying the indicators of hemocoagulation, it was found that both patients with CHD and their relatives have a tendency to hypercoagulation and a decrease in the activity of the anticoagulation system. It is noted that similar changes are also observed in the spouses of probands, although the degree of these disorders occupies an intermediate position between probands and their siblings.

The above indicates a significant role of genetic factors in the disruption of hemostasis and fibrinolysis, which can lead to coronary artery disease.

UNDERSTANDING HEMOSTASIS

The hemostasis system is a set of functional, morphological, and biochemical mechanisms that stop bleeding and, at the same time, maintain the blood in a liquid state.

The importance of the hemostasis system for maintaining the viability of the body is determined by the fact that it prevents the removal of blood from the circulatory bed and thereby contributes to ensuring normal blood supply to the organs, maintaining the necessary volume of circulating blood [2.3,4].

Mechanisms of hemostasis

It is customary to distinguish between two mechanisms of hemostasis:

1. vascular-platelet – primary, or microcirculatory;
2. Coagulation – secondary, or macrocirculatory (the process of blood coagulation and fibrinolysis).

Hemostasis links

Hemostasis is realized mainly by three interacting functional and structural components (links):

- walls of blood vessels (endothelium),
- blood cells (mainly platelets),
- plasma enzyme systems.

Each of the links of hemostasis has elements of the system that contribute to the formation of a clot (coagulants, more precisely, procoagulants) and prevent this process (anticoagulation and fibrinolytic factors):

- coagulation factors and endothelial fibrinolysis;
- platelet coagulation factors and fibrinolysis;
- erythrocyte coagulation factors and fibrinolysis;
- leukocyte coagulation factors and fibrinolysis;
- plasma coagulation factors;
- plasma anticoagulants;
- plasma fibrinolytic blood system.

The hemostasis system is subject to complex neuro-humoral regulation and the mechanisms of positive and negative feedback clearly function in it, as a result of which cellular hemostasis and blood coagulation first undergo self-activation, and then the antithrombotic potential of the blood increases. These mechanisms create conditions for the self-limitation of the coagulation process, as a result of which the local activation of the system at the sites of thrombus formation is not transformed (if the functioning of these mechanisms) into universal blood coagulation.

Until recently, the blood coagulation system played a decisive role in the implementation of hemostasis. However, modern research has again shown that the first to react to damage to blood vessels are the vessels themselves (spasm, opening of shunts above the injury site) and blood cells – platelets and, to some extent, erythrocytes. It is also known that platelets, rather than blood clotting, play a leading role in the primary control of bleeding from microvessels. (up to 100 μm in diameter), the most vulnerable and most often the source of hemorrhages. As a consequence, the vascular-platelet response to blood loss is often referred to as initial or primary hemostasis, and blood coagulation is referred to as a secondary hemostatic reaction, although both of these mechanisms are not strictly sequential to each other, but function simultaneously and conjugately over a considerable period of time.

Disorders of hemostasis lead to serious clinical consequences. An imbalance in one direction can be accompanied by excessive bleeding, in the other – by the formation of a blood clot.The walls of blood vessels play an extremely important role not only in providing chemostasis, but also in maintaining the fluid state of the blood. The intima of blood vessels and endothelium have a very high thromboresistance, due to which the preservation of this inner lining is the most important condition for maintaining the liquid state of the blood. In This thromboresistance is based on complex and not yet fully deciphered mechanisms (from the negative charge of the cytoplasmic membrane of endothelial cells to their ability to produce and secrete substances that prevent platelet aggregation, blood clotting, as well as fibrinolysis activators).

Components of hemostasis:

I. Vascular component.

1. vasospasm at the site of injury (prevention of blood loss):

a) by the mechanism of the axon-reflex,

b) serotonin, adrenaline and norepinephrine;

2. Blood bypass grafting on anastomoses above the injury site.

II. Platelet component:

1. adhesion – 3-10 sec. Normally, the vascular endothelium is negatively charged, as well as the platelet membrane, in addition, there is a secretion of prostacyclins (PGE-2), antithrombin, activators of fibrinolysis of the intima of the vessels, which prevents blood clotting.

When blood vessels are damaged, the endothelium loses its negative charge and changes it to a positive one. Negatively charged platelets adhere to the positively charged wound surface (adhesion).

Adhesion factors: excess positive charge at the site of injury; capillary subendothelial collagen – platelet activation factor; the Hagemann factor (XII); von Willebrand factor; Fibropectin is a factor in platelet spreading on the vascular wall.

2. reversible aggregation (crowding, gluing of platelets to form conglomerates of 10-20 platelets). When the platelet sticks to the injury site, they change their charge from negative to positive, and a new portion of platelets is attracted to them, which leads to the formation of a platelet aggregate. But this process is reversible, i.e. mechanical impact or an increase in blood pressure can lead to the breakdown of the platelet plug.

Aggregation factors:

electrostatic interaction;

ATP, ADP;

adrenaline;

serotonin

3. Irreversible aggregation. When platelets are activated, actin and myosin filaments contract, which leads to degranulation of platelets, the contents of the granules seem to glue the platelets into one whole.

Irreversible aggregation goes through the following stages:

a) mild metamorphosis – the formation of bridges between platelets;

b) irreversible metamorphosis – loss of platelet structure and formation of a uniform mass.

Factors:

1. thrombin (destruction of the platelet membrane);

2. platelet prothrombinase – fibrin filaments.

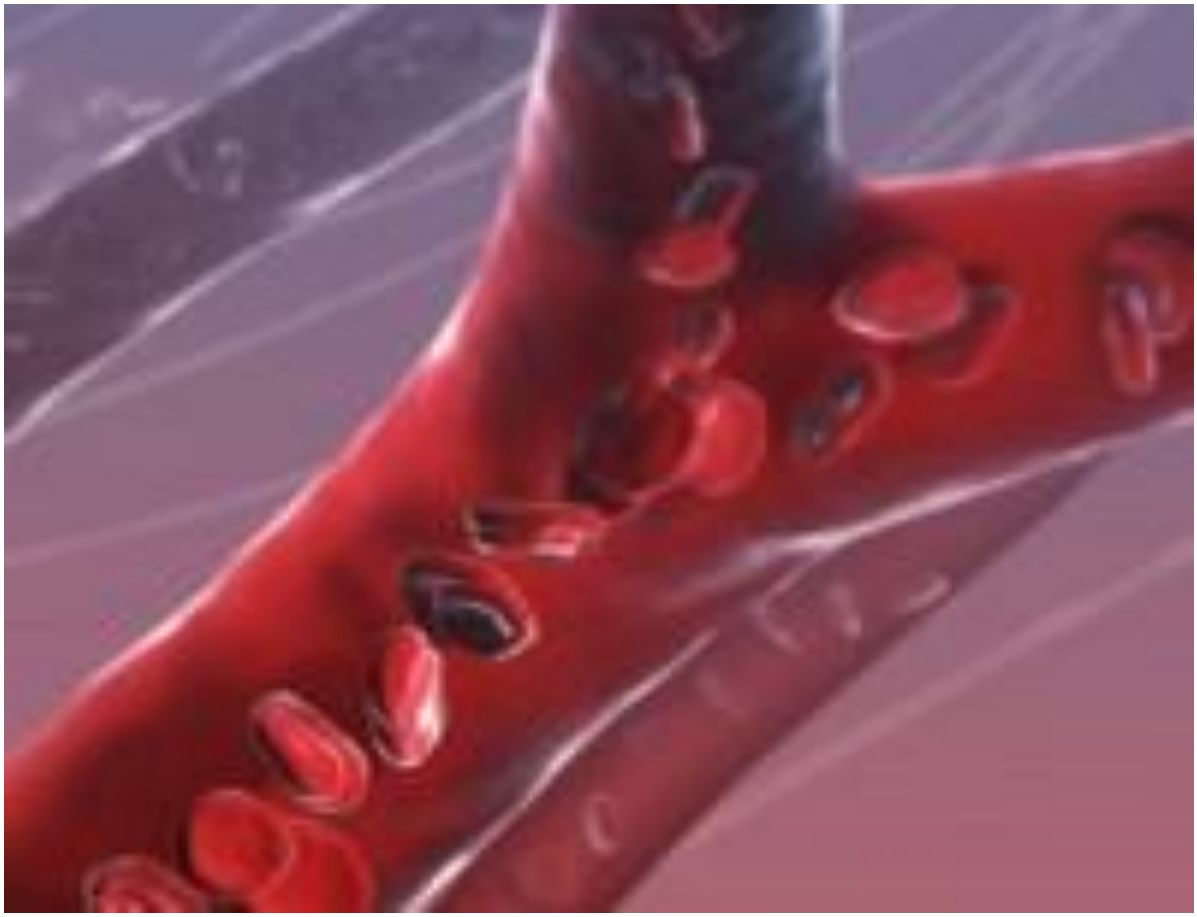
3. Platelet thrombus retraction is the strengthening and fixation of a platelet thrombus in a damaged vessel due to the actin-myosin complex of platelets under the influence of thrombosteine.

A platelet plug forms within 1-3 minutes of injury and stops bleeding from small vessels.

In large vessels, the white thrombus cannot withstand high pressure and is washed away. Therefore, hemostasis is carried out in them by the formation of a stronger fibrin thrombus (coagulation hemostasis).

Secondary hemostasis is coagulation.

The process involves the enzymatic conversion of soluble fibrinogen into insoluble fibrin to form a red blood thrombus that closes the damaged vessel. To implement coagulation, sequential (cascade) activation of coagulation factors is required.



Picture. 8 Coagulation hemostasis

Plasma coagulation factors

Plasma hemostasis is carried out mainly by proteins called plasma clotting factors. Plasma clotting factors are procoagulants whose activation and interaction lead to the formation of a fibrin clot.

According to the International Nomenclature, plasma coagulation factors are denoted by Roman numerals, with the exception of von Willebrand, Fletcher and Fitzgerald factors. To indicate the activated factor, the letter "a" is added to these numbers. In addition to the numerical designation, other names of coagulation factors are also used – according to their function (for example, factor VIII – antihemophilic globulin), according to the surnames of patients with a deficiency of one or another factor for the first time (factor XII – Hagemann's factor, X factor – Stewart-Prower factor), less often – by authors' surnames (e.g., von Willebrand factor).

Below are the main factors of blood coagulation and their synonyms according to the international nomenclature and their main properties according to the literature and special studies.

International Nomenclature of Coagulation Factors

Factor I – **fibrinogen.** It is synthesized in the liver and cells of the reticuloendothelial system (bone marrow, spleen, lymph nodes, etc.). In the lungs, fibrinogenase or fibrinodestructase

destroys fibrinogen. Plasma fibrinogen content is 2 to 4 g/l, half-life is 72 to 120 hours. The minimum level required for hemostasis is 0.8 g/L.

Under the influence of thrombin, fibrinogen is converted into fibrin, which forms the reticulated basis of the thrombus that clogs the damaged vessel.

Factor II – **prothrombin.** Prothrombin is synthesized in the liver with the participation of vitamin K. The content of prothrombin in plasma is about 0.1 g/l, the half-life is 48 to 96 hours. The level of prothrombin, or its functional completeness, decreases in endogenous or exogenous vitamin K deficiency, when deficient prothrombin is formed. The rate of blood clotting is impaired only when the concentration of prothrombin is below 40% of normal

Under natural conditions, blood coagulation under the influence of thromboplastin and calcium ions, as well as with the participation of factors V and Xa (activated factor X), united by the general term "prothrombinase", is converted into thrombin. The process of converting prothrombin to thrombin is quite complex, as the reaction produces a number of prothrombin derivatives, autoprothrombins, and finally different types of thrombin (thrombin C, thrombin E), which have procoagulant, anticoagulant, and fibrinolytic activity. Thrombin C, the main product of the reaction, promotes the clotting of fibrinogen.

Factor III – tissue thromboplastin. Tissue thromboplastin is a thermostable lipoprotein found in various organs – lungs, brain, kidneys, heart, liver, skeletal muscles. In tissues, it is not contained in an active state, but in the form of a precursor – prothromboplastin. Tissue thromboplastin**,** when interacting with plasma factors (VII, IV), is able to activate factor X, participates in the external pathway of prothrombinase formation - complex factors that convert prothrombin into thrombin.

Factor IV – calcium ions**.** Normally, the content of factor IV in plasma is 0.09 – 0.1 g/l (2.3 – 2.75 mmol/l). It is not consumed during the coagulation process. Therefore, it can be detected in blood serum. The clotting process remains normal even with a decrease in calcium concentration, in which a convulsive syndrome is observed. Calcium ions are involved in all three phases of blood clotting: activation of prothrombinase (phase I), conversion of prothrombin to thrombin (phase II) and fibrinogen to fibrin (phase III). Calcium is able to bind heparin, which accelerates blood clotting. In the absence of calcium, platelet aggregation and blood clot retraction are impaired. Calcium ions inhibit fibrinolysis.

Factor V is proaccelelin**,** plasma AC globulin**,** or labile factor. It is formed in the liver, but unlike other hepatic factors of the prothrombin complex (II, VII, and X), it is independent of vitamin K. The content of factor V in plasma is 12 – 17 U/ml (about 0.01 g/l), the half-life is 15 – 18 hours. The minimum level required for hemostasis is 10 – 15%. Factor V is required for the

formation of internal (blood) prothrombinase (activates factor X) and for the conversion of prothrombin to thrombin.

Factor VI – accelerin, or serum AC globulin – is the active form of factor V. Excluded from the nomenclature of coagulation factors, only the inactive form of the enzyme – factor V (proaccelerin) is recognized, which turns into the active form when traces of thrombin appear.

Factor VII – Proconvertin – Convertin. It is synthesized in the liver with the participation of vitamin K. It remains in stabilized blood for a long time and is activated by a wetted surface. The plasma content of factor VII is about 0.005 g/l, the half-life is 4-6 hours. The minimum level required for hemostasis is 5 – 10%. Convertin, the active form of the factor, plays a major role in the formation of tissue prothrombinase and in the conversion of prothrombin to thrombin. Activation of factor VII occurs at the very beginning of the chain reaction upon contact with a foreign surface. During the clotting process, proconvertin is not consumed and is stored in serum.

Factor VIII – antihemophilic globulin A**.** It is produced in the liver, spleen, endothelial cells, leukocytes, and kidneys. The plasma content of factor VIII is 0.01 – 0.02 g/l, the half-life is 7 – 8 hours. The minimum level required for hemostasis is 30 – 35%. Antihemophilic globulin A is involved in the "internal" pathway of prothrombinase formation, enhancing the activating effect of factor IXa (activated factor IX) on factor X. Factor VIII circulates in the blood, being bound to von Willebrand factor.

Factor IX – Christmas factor, antihemophilic globulin B**.** It is formed in the liver with the participation of vitamin K, is thermostable, and persists for a long time in plasma and serum. The plasma content of factor IX is about 0.003 g/L. Half-life is 7 to 8 hours. The minimum level required for hemostasis is 20 – 30%. Antihemophilic globulin B participates in the "internal" pathway of prothrombinase formation, activating factor X in complex with factor VIII, calcium ions, and platelet factor 3 .

Factor X is the Stewart-Prower factor. It is produced in the liver in an inactive state, activated by trypsin and an enzyme from viper venom. K-vitamin-dependent, relatively stable, half-life is 30 to 70 hours. The plasma content of factor X is about 0.01 g/L. The minimum level required for hemostasis is 10 – 20%. Factor X is involved in the formation of prothrombinase. In the current clotting regimen, active factor X (Xa) is the central factor of prothrombinase, which converts prothrombin to thrombin. Factor X is converted into an active form under the influence of factors VII and III (external, tissue, pathway of prothrombinase formation) or factor IXa together with VIIIa and phospholipid with the participation of calcium ions (internal, blood, pathway of prothrombinase formation).

Factor XI – **Rosenthal** factor, plasma precursor of thromboplastin, antihemophilic factor C. Synthesized in the liver, thermolabile. The plasma content of factor XI is about 0.005 g/l, the half-life is 30 to 70 hours. The active form of this factor (XIa) is formed with the participation of factors XIIa, Fletcher, and Fitzgerald. Form XIa activates factor IX, which becomes factor IXa.

Factor XII is the contact factor, the Hagemann factor. It is synthesized in the liver, produced in an inactive state, with a half-life of 50 to 70 hours. The plasma content of the factor is about 0.03 g/L. Bleeding does not occur even with a very deep deficiency of the factor (less than 1%). It is activated by contact with the surface of quartz, glass, cellite, asbestos, barium carbonate, and in the body by contact with the skin, collagen fibers, chondroitin sulfuric acid, micelles of saturated fatty acids. Activators of factor XII are also Fletcher factor, kallikrein, factor XIa, and plasmin. Hagemann factor is involved in the "internal" pathway of prothrombinase formation by activating factor XI.

Factor XIII – fibrin-stabilizing factor, fibrinase**,** plasma transglutaminase. It is detected in the vascular wall, platelets, erythrocytes, kidneys, lungs, muscles, placenta. In plasma, it is found in the form of a proenzyme combined with fibrinogen**.** It is converted into an active form under the influence of thrombin. In plasma, it is contained in the amount of 0.01 – 0.02 g/l, the half-life is 72 hours. The minimum level required for hemostasis is 2 – 5%. Fibrin-stabilizing factor is involved in the formation of a dense clot. It also affects the adhesion and aggregation of blood platelets. Von Willebrand factor is an antihemorrhagic vascular factor**.** It is synthesized by vascular endothelium and megakaryocytes, and is found in plasma and platelets.

Von Willebrand factor serves as an intravascular carrier protein for factor VIII. Binding of von Willebrand factor to factor VIII stabilizes the latter's molecule, increases its half-life inside the vessel, and facilitates its transport to the site of injury. Another physiological role of the relationship between factor VIII and von Willebrand factor is the ability of von Willebrand factor to increase the concentration of factor VIII at the site of vascular injury. Because circulating von Willebrand factor binds to both exposed subendothelial tissues and stimulated platelets, it directs factor VIII to the affected area, where the latter is needed to activate factor X by factor IXa.

Fletcher's factor is plasma precallicrein**.** It is synthesized in the liver. The plasma content of the factor is about 0.05 g/L. Bleeding does not occur even with a very deep deficiency of the factor (less than 1%). It participates in the activation of factors XII and IX, plasminogen, converts kininogen into kinin.

Fitzgerald's factor is plasma kininogen **(**Flożek's factor**,** Williams' factor). It is synthesized in the liver. The plasma content of the factor is about 0.06 g/L. Bleeding does not occur even with

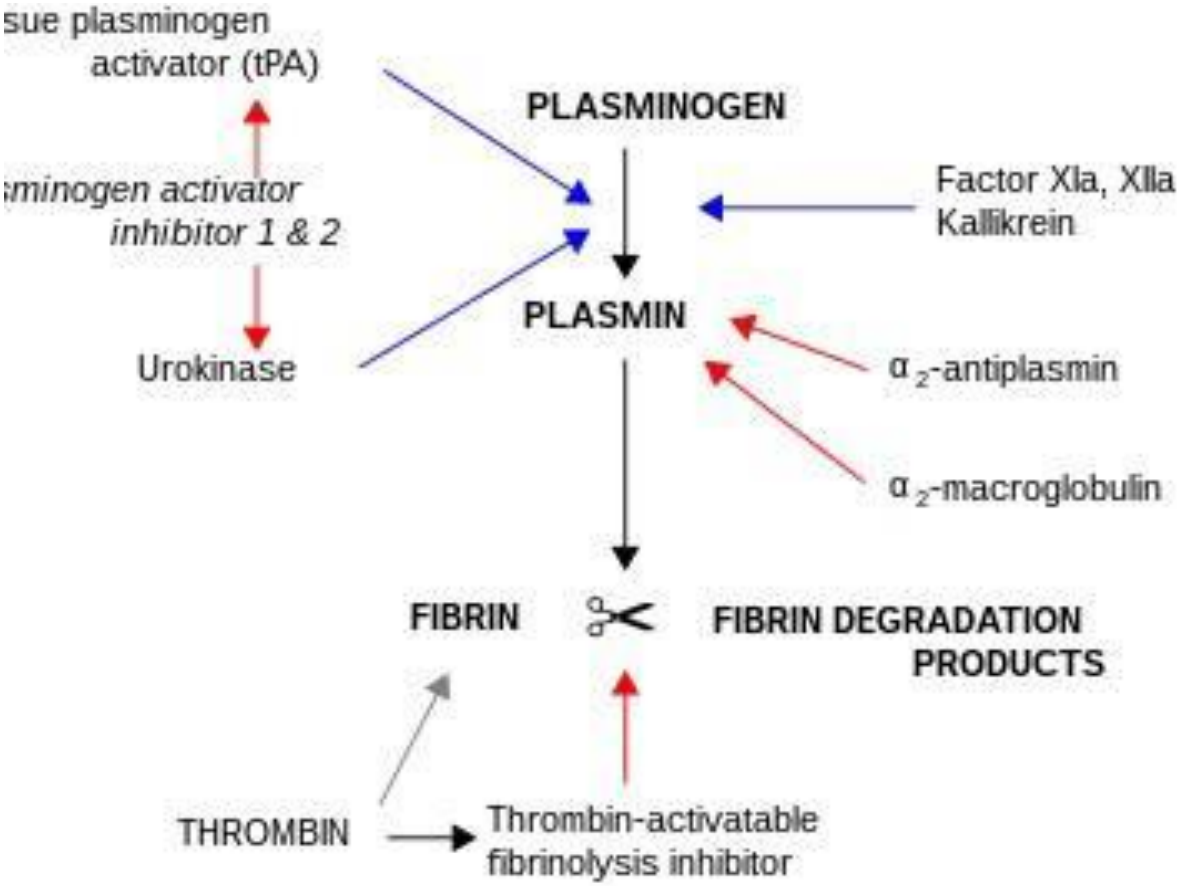
a very deep deficiency of the factor (less than 1%). Participates in the activation of factor XII and plasminogen [8,9,10].

UNDERSTANDING FIBRINOLYSIS

Fibrinolysis (from fibrin and Greek lýsis – decomposition, dissolution) is the process of dissolving blood clots and blood clots, an integral part of the hemostasis system, which always accompanies the process of blood clotting and is cultivated by factors involved in this process. It is an important protective reaction of the body and prevents fibrin clots from clogging blood vessels.

Fibrinolysis also contributes to the recanalization of blood vessels after the bleeding stops. It involves the breakdown of fibrin by the action of plasmin present in blood plasma in the form of an inactive precursor - plasminogen. The latter is activated at the same time as the blood clotting process begins.

Fibrinolysis, like the process of blood clotting, proceeds through an external or internal mechanism. The external pathway of activation is carried out with the integral participation of tissue activators synthesized mainly in the vascular endothelium.



Picture. 9. Fibrinolysis scheme. Blue arrows - stimulation; Red Arrows - Suppression

These activators include tissue plasminogen activator (tPA) and urokinase. The internal mechanism of activation is carried out by plasma activators and activators of formed blood elements — leukocytes, platelets and erythrocytes. The internal activation mechanism is divided into Hageman-dependent and Hageman-independent. Hageman-dependent fibrinolysis occurs under the influence of clotting factor XIIa, kallikrein, which causes the conversion of plasminogen to plasmin. Hageman-independent fibrinolysis is the most rapid. Its main purpose is to cleanse the vascular bed of unstabilized fibrin, which is formed in the process of intravascular blood clotting.

There are also other stimulators of fibrinolysis in the blood: urokinase, an enzyme produced in the kidneys, trypsin, acid and alkaline phosphatase, and the kallikrein-kinin system. The main regulators of fibrinolysis are the tissues themselves, especially the vascular walls, which contain tissue lysokinases that enter the blood and convert the blood proactivator into an activator. Fibrinolysis activators have been found in tissues that act directly on plasminogen, converting it into plasmin (a direct activation pathway).

Fibrinolysis occurs in three phases:

In phase I, a blood plasminogen activator is formed from a blood proactivator.

In phase II, the blood plasminogen activator, together with other stimulants (urokinase, alkaline and acid phosphatase, etc.), converts plasminogen into the active form, plasmin.

In phase III, plasmin breaks down fibrin into peptides and amino acids.

Each phase of the fibrinolytic process has its own inhibitors: antilysokinases, antiactivators, antiplasmins.

In the body, in addition to enzymatic fibrinolysis, there are mechanisms of non-enzymatic fibrinolysis, which is carried out by complexes: heparin with epinephrine, fibrinogen, fibrinase and antiplasmin, which inhibit blood coagulation and lyse (dissolve) fibrin prestages.

The blood is in the vascular bed in a liquid state due to the presence of two antagonistic systems in it, which perform specific functions: the coagulation and anticoagulation systems.

The latter is the main system that maintains homeostasis. Maintaining the blood in a liquid state is facilitated by:

1. Smooth vascular endothelial surface that prevents Hagemann factor activation and platelet aggregation.
2. Sameness of vessel wall charges and formed elements (negative).
3. Soluble fibrin, which coats the walls of blood vessels and adsorbs active coagulation factors, especially thrombin.

4. High velocity of blood flow, which does not allow hemocoagulation factors to reach the required concentration in one place.

5. Presence of natural anticoagulants in the blood.

I. P. Pavlov found that the blood flowing from the lungs coagulates more slowly than the blood flowing to them, which is explained by the presence of anticoagulants in the blood, i.e. substances that prevent blood clotting.

There are a number of substances in the body that prevent blood clotting, which can be divided into primary and secondary.

Primary, or preceding, which include antithromboplastins that inhibit the activity of prothrombinase; antithrombins, the most active of which are antithrombin III and antithrombin IV (a2-macroglobulin). Particularly active primary anticoagulants include heparin, secreted by basophils and mast cells of connective tissue. Heparin blocks all phases of hemocoagulation and stimulates fibrinolysis in small doses, inhibits hyaluronidase activity, reduces the permeability of the vascular walls, inhibits the antigen-antibody reaction, and has analgesic and anti-inflammatory effects.

Secondary anticoagulants are formed in the process of blood coagulation and fibrinolysis and are products of the metabolism of coagulation factors. For example, fibrin, which adsorbs and neutralizes up to 90% of thrombin, is called antithrombin-1. At rest, the content of anticoagulants increases slightly, but dramatically, in response to factors that cause an acceleration of blood clotting. It has been established that pain factors, emotions (fear and anger) and reactions associated with the activation of the sympathetic part of the autonomic nervous system and hyperadrenaline increase the blood coagulation response due to the longest phase of hemocoagulation — the formation of prothrombinase.

Thus, the regulation of blood coagulation is carried out mainly by the neurohumoral pathway. Adrenaline and norepinephrine released into the bloodstream stimulate tissue and plasma reactions, namely:

1. Release of thromboplastin from the vascular wall, which is rapidly converted into prothrombinase in the blood.

2. Activate Hagemann factor, which affects the formation of blood prothrombinase.

3. Stimulate the appearance of tissue lipases in the blood, which break down fats, enhancing their thromboplastic activity.

4. Activate the release of phospholipids from erythrocytes and other formed elements of the blood.

The combination of these reactions ultimately leads to the consumption of coagulation factors, with the cessation of the action of which the anticoagulation system is activated. At this time, there is an increase in fibrinolysis, leading to the destruction of excess fibrin.

The coagulation system is part of the system for regulating the aggregate state of blood and colloids, which maintains homeostasis.

Inhibition of fibrinolysis

The fibrinolytic activity of the blood is largely determined by the ratio of inhibitors and activators of the fibrinolysis process.

There are also inhibitors of fibrinolysis in the blood plasma, which suppress it. One of the most important such inhibitors is α2-antiplasmin, which causes the binding of plasmin, trypsin, kallikrein, urokinase, tissue plasminogen activator.

Thus, inhibiting the process of fibrinolysis in its early and late stages. The α1-protease inhibitor is also a strong inhibitor of plasmin. Fibrinolysis is also inhibited by alpha2-macroglobulin, a C1-protease inhibitor, and a number of plasminogen activator inhibitors produced in the endothelium, as well as fibroblasts, macrophages, and monocytes.

Regulation of fibrinolysis

A balance is maintained between blood clotting processes and fibrinolysis in the body. Increased fibrinolysis is due to an increase in the tone of the sympathetic nervous system and the entry of adrenaline and norepinephrine into the blood. This triggers the activation of Hagemann factor, which triggers the external and internal mechanisms of prothrombinase production, and also stimulates Hageman-dependent fibrinolysis. The endothelium also secretes tissue plasminogen activator and urokinase, which stimulate the process of fibrinolysis.

In addition to fibrinolysis, autolysis of fibrin (due to enzymes of erythrocytes and leukocytes) can occur - aseptic autolysis, or - dissolution of fibrin by ferants of staphylo- and streptococci - septic autolysis.

If there are no conditions for fibrinolysis, then either organization (replacement by connective tissue) or recanalization (formation of a channel inside the thrombus) occurs. In some cases, a blood clot can break away from the site of its formation and cause a blockage of the vascular bed (embolism), which can lead to death. With an increase in the tone of the parasympathetic nervous system, there is also an acceleration of blood coagulation and stimulation of the fibrinolysis process.

The main efferent regulator of blood coagulation and fibrinolysis is the vascular wall.

Blood types.

1901 – K. Landsteiner discovers the AB0 blood group. In 1927, together with Levin, he discovered the factors N, M, and P. 1937-40 – Together with A. Wiener, he discovered the Rh factor. At present, more than 250 group antigens are known, combined into systems. More than 15 such systems are known for erythrocytes.

AB0 system.

According to the classification of K. Landsteiner and J. Jansky, there are 4 blood groups.

Blood type	Agglutinogens on the erythrocyte membrane (A, B)	Plasma agglutinins (α, β)
I (0)	—	α, β
II (A)	A	β
III (B)	B	α
IV (AB)	A, B	—

Agglutination occurs when agglutinogen and agglutinin of the same name occur in a person's blood:

A + α = agglutination;

B + β = agglutination.

When incompatible blood is transfused, blood transfusion shock develops as a result of agglutination and subsequent hemolysis, which can lead to death. Therefore, the rule is currently adhered to according to which only single-group blood is transfused.

Rhesus system. It was discovered as a result of immunization of rabbits with the blood of rhesus monkeys (Landsteiner, Wiener, 1937-40).

The modern variant of the antigens of this system is a combination of the Landsteiner-Jansky and Fischer-Rice nomenclatures.

Antigens.

D (Rh0) d (Hr0)

C (Rh') c (hr')

It's (Rh') and (hr')

The most active antigen is D, which is detected in 86% of Europeans and 100% of.

The Rh system, unlike the AB0 system, does not normally have the corresponding agglutinins in plasma. However, if the blood of an Rh (+) donor is transfused to an Rh (-) recipient, then specific antibodies – anti-Rh agglutinins – are formed in the body. In case of repeated transfusion of Rh(+) blood to this recipient, an Rh conflict occurs, proceeding in the form of blood transfusion shock. Therefore, only Rh(-)- blood can be transfused into recipients.

Rh conflict can also occur during pregnancy. If a mother with Rh(-) blood develops an Rh(+) fetus, then the first pregnancy usually does not cause an Rh conflict, because the erythrocytes of the fetus do not enter the mother's body. During childbirth, it is possible to immunize the mother's body with fetal erythrocytes, which will lead to the formation of antibodies to Rh(+) red blood cells. In the case of repeated pregnancies, antibodies from the mother's body easily cross the placental barrier into the fetus, which leads to miscarriage or hemolytic disease of the newborn. For the purpose of immunoprophylaxis of Rh conflict, a woman is injected with concentrated anti-D antibodies immediately after childbirth or abortion.

Other systems.

Antigenic systems of erythrocytes.

1. The Lewis system is a fairly active system that manifests itself when
2. Blood transfusion and pregnancy system
3. Kell System
4. Daffy system (Fy)
5. Kidd System
6. Lutheran System (Lu) Systems Relevant in Transplantation
7. Ai system of organs and tissues
8. Diego's system
9. Oberni system
10. Dambran System
11. MNSS
12. Lewis system (Le)

Leukocyte antigenic systems.

White blood cells have more than 90 antigens. Some of them are erythrocyte antigens of the AB0, Kidd, and Duffy systems, with the exception of the Rh system.

In addition, leukocytes contain HLA (Human Leycocit Antigen) main cone antigens, called histocompatibility antigens, which play a leading role in transplant immunity.

Methods for determining blood groups.

I. With the help of standard serums.

To determine blood groups according to the AB0 system using standard serums, serums of groups I, II, III of two series are used. The reaction is carried out at room temperature. The ratio of serum to red blood cells is 10:1.

II. Method of determining blood groups according to the AB0 system using zoliclons.

There is a modern method based on the use of monoclonal antibodies – zoliclone anti-A, zoliclone anti-B. This method avoids errors that may occur due to the presence of weak antigens Tzoliclones are markers of the corresponding agglutinogens, i.e. agglutination occurs when interacting:

anti-A zoliclone with agglutinogen A;

anti-B zoliclone with agglutinogen B.

III. Methods for determining blood groups according to the Rh system.

To determine Rh affiliation, i.e. to detect antigens of the Rh system in erythrocytes, standard anti-Rh serums containing antibodies to different antigens of this system are used. To determine the D antigen, anti-Rh serum with the addition of a 10% gelatin solution is more often used, or a standard anti-Rh reagent prepared on the basis of a 33% polyglukin solution is used.

Platelets.

Platelets are non-nucleated fragments of the cytoplasm of megakaryocytes, which, despite lacking the ability to synthesize DNA, have many functions and a complex metabolism. These are flat cells of irregular rounded shape, with a diameter of 2-5 μm, in humans they do not have a nucleus, 2/3 of the blood platelets circulate in the blood, the rest are deposited in the spleen. The lifespan is 8 days. Quantity: 180-320*109/l.

Increase in number – thrombocytosis; Decrease in the number of thrombopenia.

To fully ensure the physiological role of the primary link of hemostasis, both the number of platelets and their functional (qualitative) state are important. Platelets have three types of granules ά – they accumulate and synthesize proteins – fibrinogen, von Willebrand factor, platelet factor 4, thromboglobulin and platelet growth factor. Dense granules accumulate smaller molecules – Ca2+, ADP, biogenic amines (serotonin, catecholamines, etc.). Lysosomal granules contain acid hydrolases. In the membrane of platelets, many receptors are localized (5 types of glycoprotein receptors, receptors for collagen, thrombin, ADP, catecholamines, serotonin, thromboxane A2, platelet activation factor, Fc-fragment of immunoglobulins, complement components, insulin, ά-adrenoreceptors, receptors for endothelin), receptor-like proteins that bind and hold complexes of coagulation factors and integrins on the surface of platelets, which participate in cellular Adhesion.

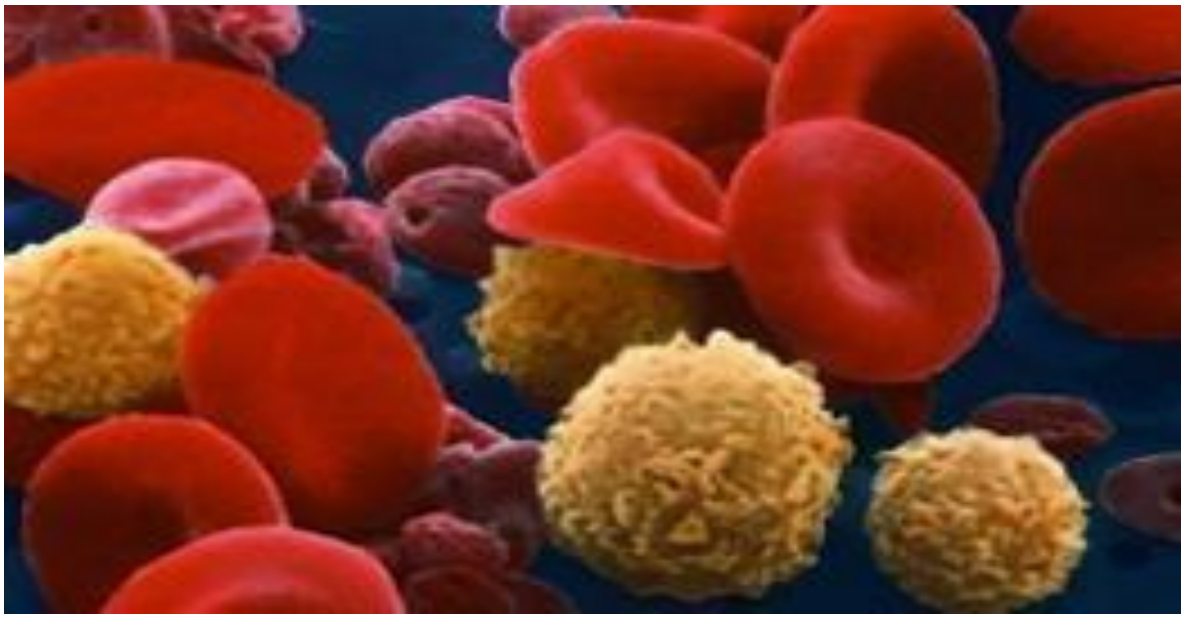
Platelet function.

Platelets have a number of ***functions***:

- ***angiotrophic (***nourishment of the vascular endothelium) or ***angioprotective ability*** (maintenance of the normal structure and function of microvessels, their resistance to damaging effects, preventing the penetration of erythrocytes outside the vessels);
- the ability to maintain the spasm of damaged vessels by ***secreting (releasing) vasoactive substances (***adrenaline, norepinephrine, serotonin and other amines);
- ***formation, deposition and transport of*** substances that stimulate platelet adhesion and aggregation;
- ***adhesive-aggregation function***, which provides primary bleeding control by forming a primary platelet plug due to adhesion (*adhesion) of* platelets to the endothelium and their gluing *(aggregation)* to each other;
- ***participation in hemocoagulation processes, primarily due to the isolation of platelet coagulation factors, the most important of which is membrane phospholipid factor 3, which serves as a matrix for the interaction of plasma hemocoagulation*** factors and the formation of their active complexes. In terms of its properties, this component is identical to cephalin and erythrocyte membrane factor – erythrocytin. No less important is the 6th platelet factor – retractosisyme, which is necessary for the reduction and fibrin clot hardening. Platelets also have activators for the polymerization of fibrin monomers, factor V, and many plasma clotting and fibrinolysis factors are concentrated on the surface and in their channels. Due to this, a high concentration of them is created in the

hemostatic plug (prothrombin, thromboplastin, Ac-globulin, convertin, factors II, III, V, VIII, IX, X, XI, XII, plasminogen, etc.). Therefore, platelets most significantly affect the intensity and speed of local coagulation in the area of thrombus formation, and not the blood clotting process in general.

The formation of a primary thrombus takes place in three stages, provided by platelets:



Platelets in the blood

- Platelet adhesion is the adhesion of platelets to subendothelial components (in particular, collagen) or to a foreign surface (e.g., glass, beads). At the same time, there is a change in the charge (from "-" to "+") of the endothelial cells of the damaged vessel (this reduces the mutual repulsion of platelets, which are charged with "-" and endotheliocytes). The duration of this phase is 1-3 seconds. Platelet adhesion to the subendothelium of damaged blood vessels It is primarily due to the interaction of its three components: specific receptors of platelet membranes (glycoprotein Ib, IIb, IIIa), collagen and von Willebrand factor. It is the von Willebrand factor and some other proteins (such as thrombospondin, fibronectin) involved in the process of adhesion of blood platelets that form a kind of bridges between the collagen of the vascular subendothelium and the receptors (I b) of platelets (Fig. 15).

- platelet activation and degranulation ***(platelet release reaction) of platelets (Fig. 16).*** Activation of platelets leads to a change in the traditional disc-shaped shape of platelets to a spherical one, the formation of processes (pseudopodia) and adhesion of platelets to the structures of the subendothelium, in particular to collagen. The activation of blood platelets results in their initial aggregation and the release of a number of active substances from them, which serve as strong platelet stimulators (ADP, serotonin, epinephrine, unstable prostaglandins,

thromboxane A2, platelet-activating factor, etc.) . Somewhat later, granules containing lysosomal enzymes are secreted.

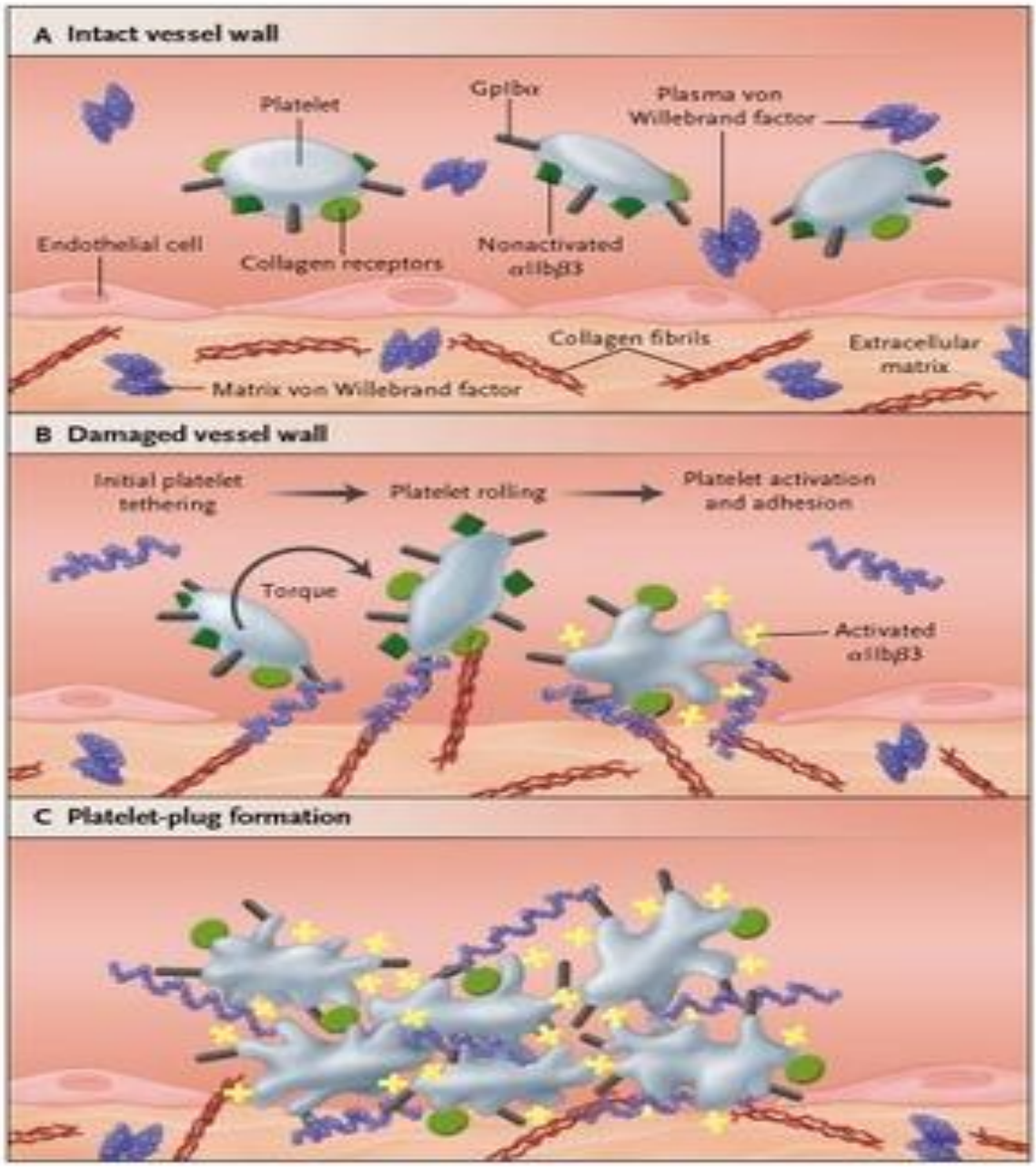
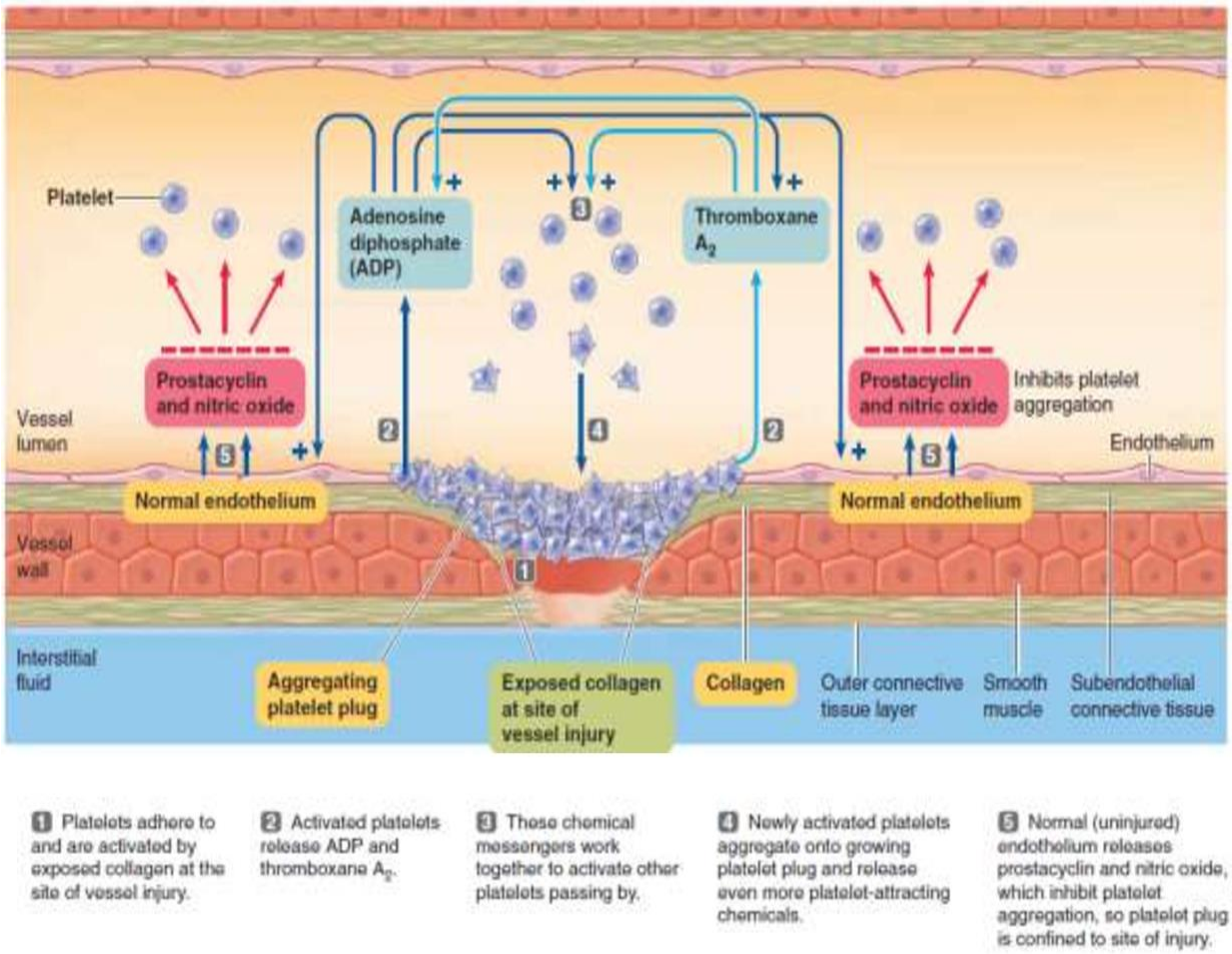


Fig 10. Formation of "bridges" between collagen fibers and platelet receptors



Picture. 11. Effects of the reaction of release of biologically active substances from damaged tissue and platelets. ADP – adenosine diphosphate, CA – catecholamines, C – serotonin

- platelet aggregation is the adhesion of platelets to each other under the influence of specific stimulants.

A distinction is made between aggregation: reversible; Irreversible.

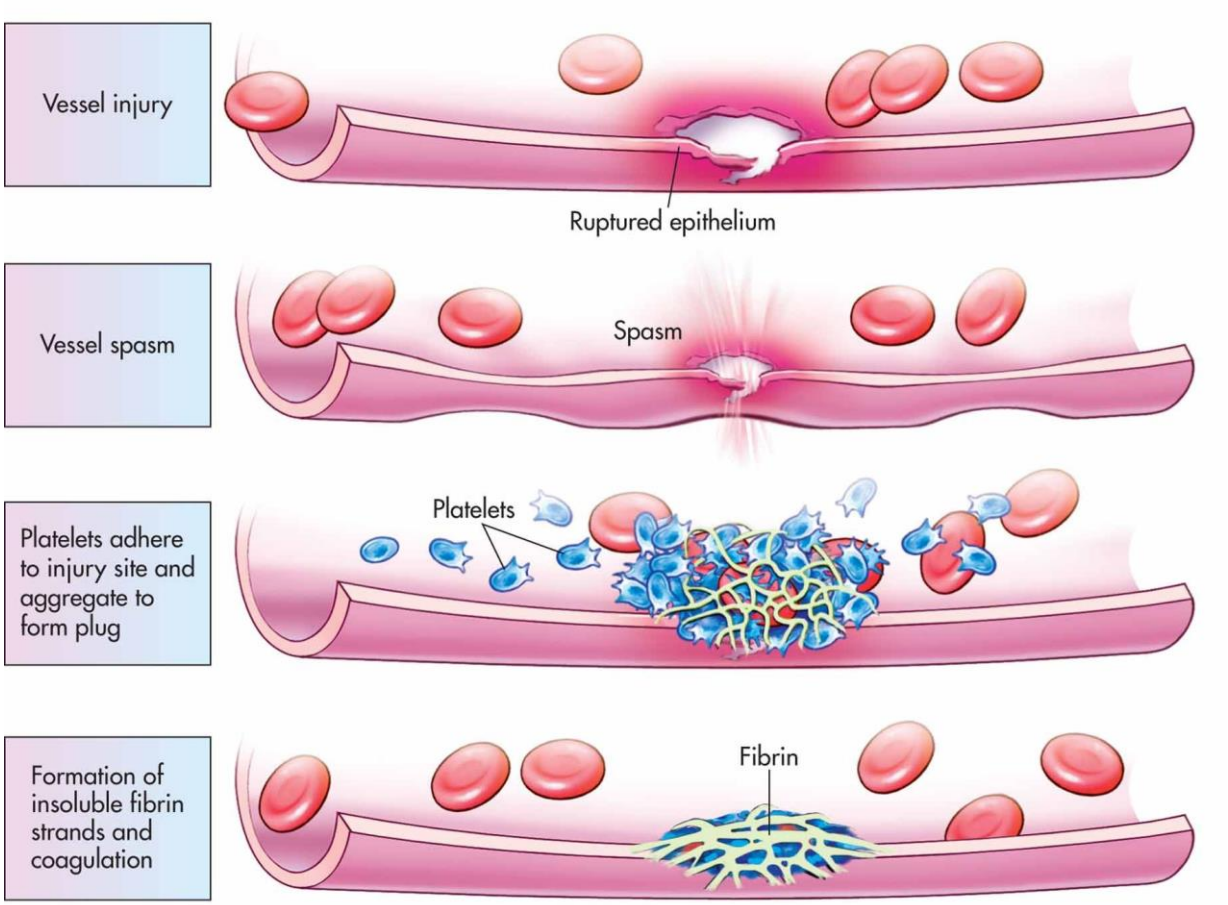
Reversible aggregation is the accumulation of platelets at the site of injury and their adhesion to each other. Aggregation begins almost simultaneously with adhesion and is caused by the release of biologically active substances (primarily ATP and ADP) by the damaged vessel wall, as well as platelets and erythrocytes. As a result, a loose platelet plug is formed, which is permeable to blood plasma.

Irreversible aggregation is the aggregation of blood platelets, in which they lose their structure and merge into a homogeneous mass, forming a plug that is impermeable to blood plasma. This reaction occurs under the influence of thrombin, which destroys the membrane of platelets, which leads to the release of biologically active substances from them: serotonin, histamine, enzymes and blood coagulation factors. Their release contributes to secondary vasospasm. The release of platelet factor 3 gives rise to formation of platelet prothrombinase, i.e., activation of

the mechanism of coagulation hemostasis. A small number of fibrin filaments are formed on platelet aggregates, in the networks of which the formed blood elements are retained.

In the regulation of platelet hemostasis, an important role is played by derivatives of arachidonic acid, which is released from the membrane phospholipids of platelets and the vascular wall due to the activation of phospholipases. Under the influence of cyclooxygenase, prostaglandins are formed, from which an extremely powerful aggregating agent, thromboxane-A2, is formed in platelets under the influence of thromboxane synthetase. The lifespan of thromboxane, prostacyclin and other prostaglandins is several minutes, but their importance in the regulation and pathology of hemostasis is very high. This mechanism is a trigger in the implementation of the adhesive-aggregation function of platelets. To perform this function of blood platelets, a number of plasma aggregation cofactors are required: calcium and magnesium ions, fibrinogen, albumin, and two protein cofactors, designated as agrexones A and B, a phospholipid cofactor, etc. At the same time, paraproteins, cryoglobulins, and fibrinolysis products inhibit platelet aggregation.

Schematically, vascular-platelet hemostasis can be represented as follows:



Picture. 12. Scheme of vascular-platelet hemostasis (source: http://smed.ru)
1 – endothelial damage; 2 – platelet adhesion; 3 – activation of platelets, isolation of biologically active substances from their granules and formation of mediators – arachidonic acid derivatives; 4 – change in the shape of platelets; 5 – irreversible aggregation of platelets with subsequent thrombus formation.EF – von Willebrand factor, TGF – platelet growth factor, TXA_2 – thromboxane A2 , ADP – adenosine diphosphate, FAT – platelet activation factor.

Disorders that develop at any of these stages can lead to bleeding.

How does the bleeding stop occur in the first place?

Mechanism of primary bleeding control.

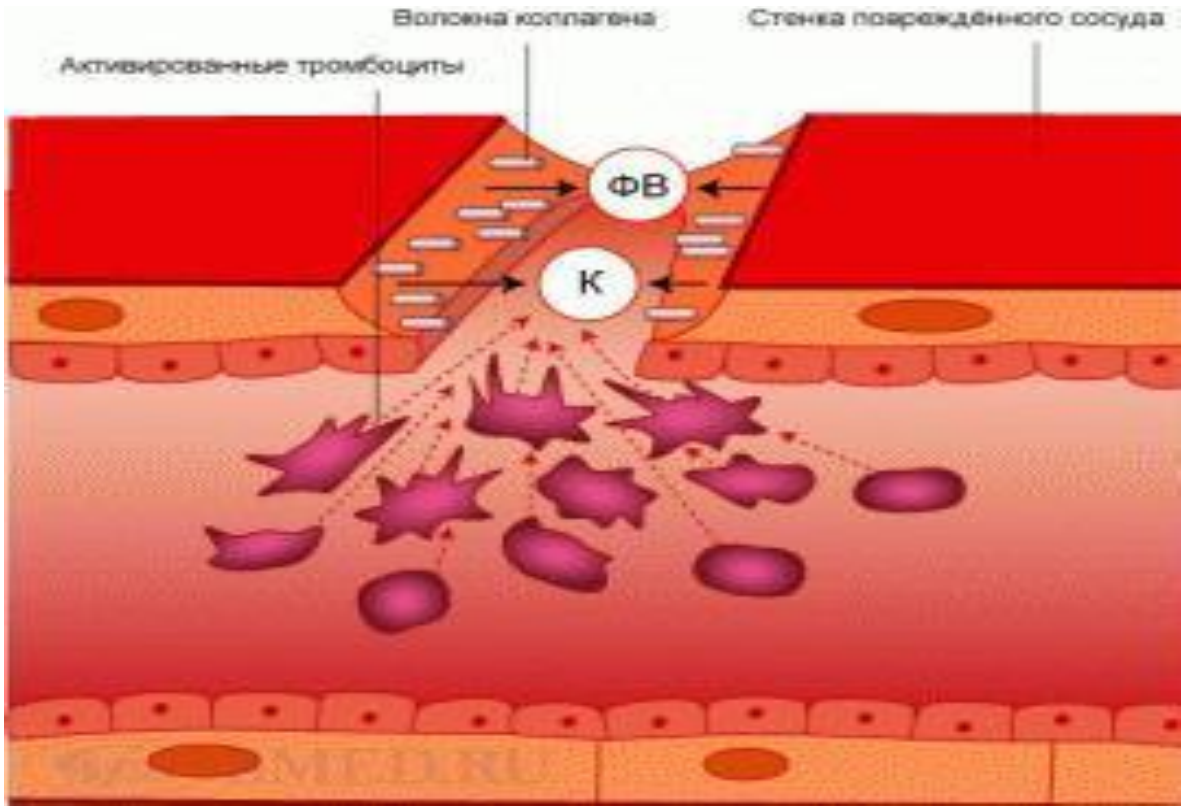
Damage to the walls of blood vessels (Fig. 13) and exposure of subendothelial tissue structures, primarily collagen, play a triggering role in the implementation of the vascular-platelet link of hemostasis.

Picture. 13. Vascular wall damage

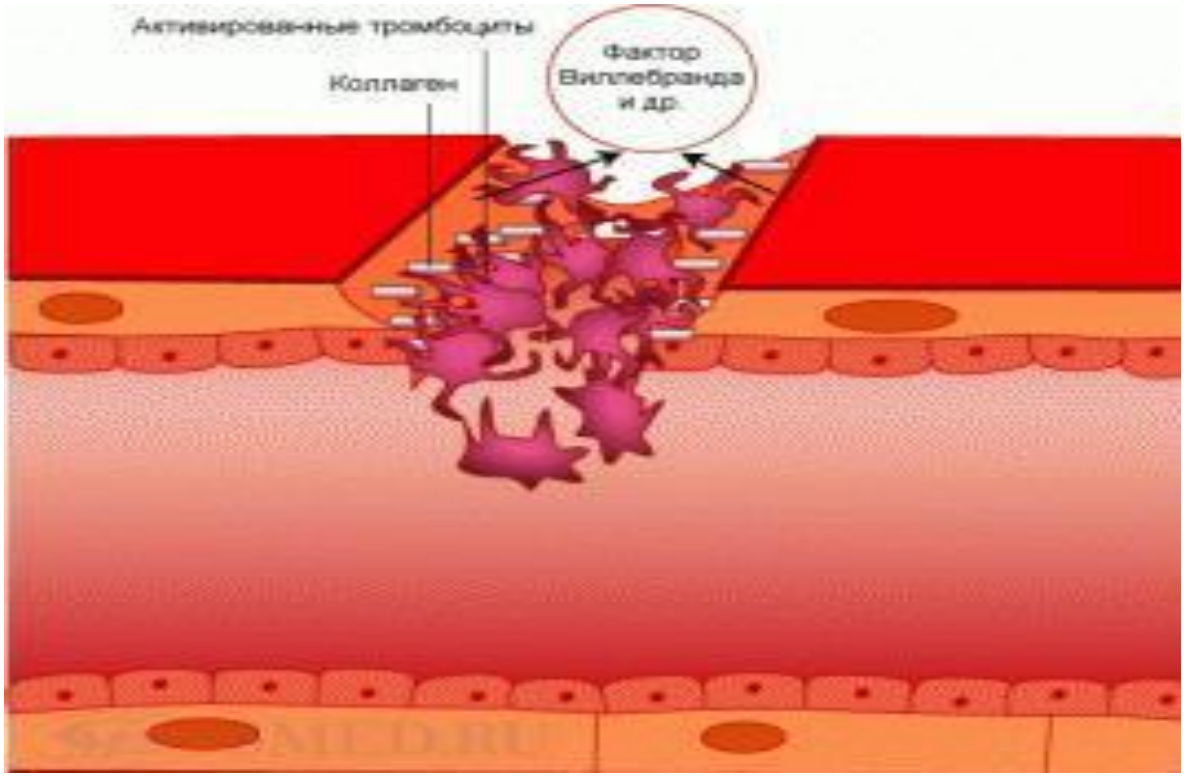
Under the influence of collagen and von Willebrand factor (VF) contained in the subendothelium, platelets are rapidly activated, which, changing their shape, swelling and forming spike-like processes, adhere (adhesion) to the fibers of connective tissue at the edges of the wound. At the same time, the collagen of the subendothelium and the locally formed thrombin induce the release of the contents of platelet granules. The von Willebrand factor released in this case potentiates adhesion, vasoconstrictor substances (serotonin, catecholamines,

platelet growth factor – TGF) cause a decrease in the lumen of blood vessels, and, accordingly, a slowdown in blood flow.

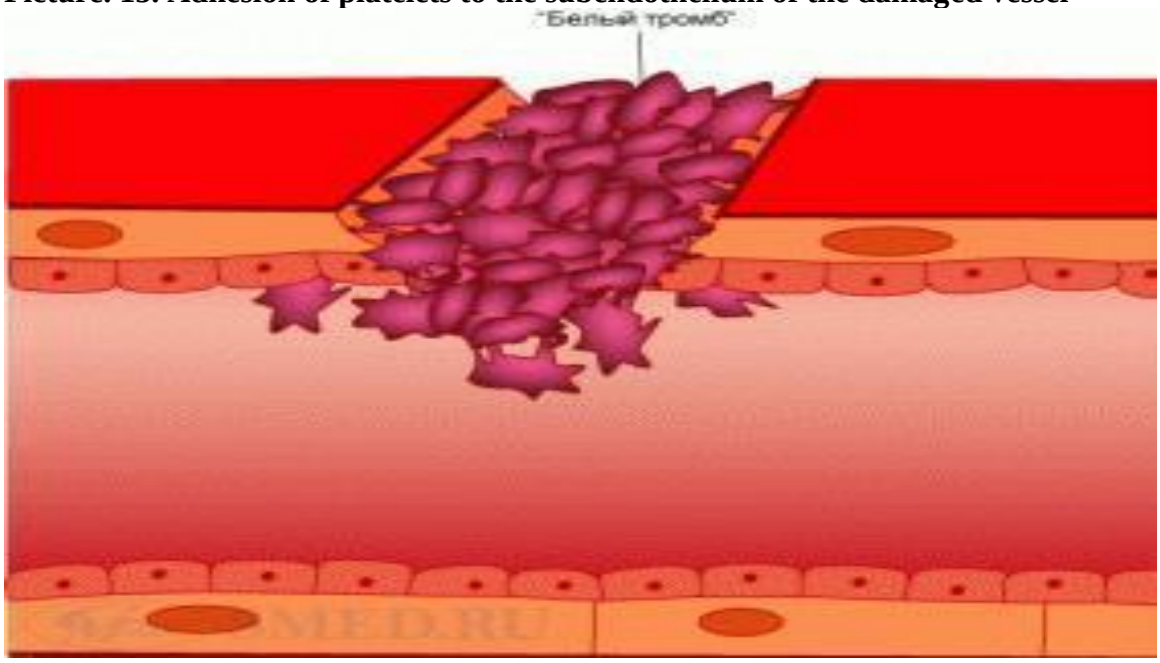
Platelet adhesion to the subendothelium is very rapid and is usually completed in the first 3-10 seconds. from the moment the vessel is damaged. The adhesion of platelets to the vascular wall leads to swelling and adhesion of blood platelets to each other (this is facilitated by the spike-like processes of platelets), aggregates consisting of 3-20 cells are formed. These aggregates are superimposed on the primary adhesion cells, i.e. in fact, blood platelets are superimposed on the site of vascular damage. As a result of this overlap, a primary thrombus consisting only of platelets is formed, which completely closes the lumen of the bleeding vessel (Fig. 14).



Picture. 14. Platelet activation by collagen (K), exposed subendothelial tissue structures and von Willebrand factor (FV)



Picture. 15. Adhesion of platelets to the subendothelium of the damaged vessel



Picture. 16. Platelet aggregation and formation of primary (platelet) thrombus

At the same time, as a result of the reaction of release of biologically active substances from platelets and damaged vascular cells, 2 important effects develop:

- spasm of the damaged microvessel (under the influence of serotonin, adrenaline and other biologically active substances);

- a sharp increase in the process of platelet aggregation (as a result of the action of ADP, serotonin and adrenaline).
- As a result, there is a limitation of the initial loss of blood from the wound; local accumulation of hemostatic substances.

Subsequently, there is a retraction of the platelet thrombus – its thickening and fixation in the damaged vessels due to the reduction of the actomyosin-like protein (contains subunits A and M, similar to actin and myosin) of the platelet protein – thrombostenin (ATP-dependent process), which ensures the squeeze and thickening of the thrombus.

As a result of the described processes, an unstable, loose white platelet thrombus is formed, which can stop bleeding from the vessels of the microcirculatory bed, but without further participation of the coagulation link of hemostasis, it is not able to provide a complete stop of bleeding from large vessels (with a high linear velocity of blood movement or with high pressure - there it is destroyed due to insufficient mechanical strength).

It is important to know that:

1. The physiological role of the vascular-platelet link of hemostasis is the primary control of bleeding by the formation of an unstable primary (platelet) thrombus.
2. The initial stop of bleeding normally occurs in 2-4 minutes.
3. The most important factors providing primary (vascular-platelet) hemostasis are platelets and von Willebrand factor, which promotes their adhesion and aggregation.
4. Primary hemostasis is the first step in stopping bleeding and is not able to provide definitive control of bleeding in medium- and large-caliber vessels.
5. Vascular-platelet and coagulation hemostasis are interrelated, but still relatively independent, processes.

In addition to platelets and the vascular wall, other formed elements of the blood, in particular erythrocytes and leukocytes, are involved in providing primary hemostasis. Both erythrocytes and leukocytes contain compounds, some of which are similar to platelet factors. At the same time, these formed elements are able to adsorb and accumulate plasma coagulation and fibrinolysis factors, as well as anticoagulants. And yet, The role of erythrocytes and leukocytes in hemostasis is not yet well understood.

Erythrocytes

It is known that erythrocytes enter the hemostatic process in its early stages. In these formed elements, a distinction is made between intraerythrocyte factors belonging to any of the erythrocyte structures and extraerythrocyte plasma coagulation and fibrinolysis factors, as well as anticoagulants.

Intraerythrocytic factors include a number of factors:

- ***Thromboplastic factor (erythrocytin).*** This is the most important factor in red blood cells. It is a thermostable phospholipid that is part of the membrane and affects the blood coagulation process regardless of the presence of tissue thromboplastin and platelets. It is similar in properties to platelet factor 3.

Erythrocytin is an endogenous red blood cell factor. It is involved in the formation of prothrombinase in the internal clotting mechanism of blood. The activity of erythrocytin excretion into plasma depends on the level of a number of substances, in particular mediators and hormones (epinephrine, norepinephrine, acetylcholine, histamine and thrombin). This is due to the effect of these substances on the permeability of the erythrocyte membrane for ions, their osmotic resistance, and a decrease in the electrophoretic mobility of erythrocytes, which is a consequence of a decrease in the negative electrokinetic charge. It has been proven that erythrocytin is most active during massive destruction (i.e. hemolysis) of erythrocytes.

- ***Anti-heparin factor.*** It is assumed that the erythrocyte antiheparin factor is capable of being released into the plasma. Both destroyed and intact erythrocytes have this activity.
- ***Ac-globulin (accelelin)*** is a compound similar to plasma factor V. It is found in destroyed as well as intact red blood cells.
- ***Thrombin-like factor*****.** It promotes the conversion of fibrinogen into fibrin. It is similar in properties to platelet factor 2.
- ***Fibrinstabilizing factor***. This factor is found in hemolyzed and, to a lesser extent, intact red blood cells. It participates in the formation of dense stabilized fibrin insoluble in 5M urea solution.
- ***ADP (adenosine diphosphate).***It enhances the adhesion and aggregation of platelets. Destroyed erythrocytes have a stronger effect on the adhesive-aggregation activity of platelets than intact ones. It has been revealed that erythrocytes themselves are also subject to adhesion and aggregation. It is believed that this process occurs normally, i.e. it is physiological (reversible) in nature. In conditions of pathology, it becomes irreversible.
- ***Antithromboplastic factor***. This factor is found in red blood cell hemolysate. Its properties are similar to those of an anticoagulant: it dramatically slows down and sometimes completely prevents blood clotting. The presence of heparin in plasma does not affect the antithromboplastic activity of erythrocytes.
- ***The red blood cell factors influencing blood clot retraction*** are actually contractile proteins of red blood cells resembling the actomyosin of muscle fibers.

- ***Fibrinolysis factors.*** These factors are activators of fibrinolysis. They are partly found inside red blood cells and partly adsorbed from plasma. Plasminogen proactivators have been found in hemolysate and stroma, which contribute to the dissolution of the blood clot, in particular erythrokinase. If the formation of a blood clot is accompanied by hemolysis, then the released proactivator and plasminogen activator contribute to the rapid thinning of the blood.
- ***Fibrinolysis inhibitors*.** They are found both inside red blood cells and adsorbed from plasma. Inhibitors neutralize plasminogen proactivators and activators, as well as plasmin itself.

Thus, destroyed red blood cells mainly stimulate fibrinolysis, while intact red blood cells inhibit it. That is, under natural conditions, the inclusion of red blood cells in a blood clot makes the latter more resistant to plasmin.

It is known that when a vessel is injured, about 1% of the least resistant erythrocytes of the leaking blood are destroyed, which contributes to the formation of a platelet plug and a fibrin clot. Erythrocytes play a particularly active role in blood coagulation in the event of their mass destruction (transfusion of incompatible blood, Rh conflict between mother and fetus, hemolytic anemia, etc.).

Of the extra-erythrocyte factors, the following factors are the most important:

- ***Erythrocyte fibrinogen***.It is known that the erythrocyte adsorbs a significant amount of plasma fibrinogen on its surface. The negative charge of red blood cells plays an important role in the process of fibrinogen binding. Fibrinogen itself has also been shown to have a negative charge. It is assumed that adsorption occurs due to sections of the fibrinogen molecule with positively charged prosthetic groups. This mechanism is able to regulate the concentration of fibrinogen in the blood.

Fibrinogen has been shown to play an important role in the mechanism of red blood cell aggregation. In addition, as a result of the action of thrombin, fibrinogen adsorbed on the surface of erythrocytes coagulates, as a result of which erythrocytes are firmly fixed between fibrin strands.

- ***Antithrombins***. Erythrocytes also adsorb heparin on their surface, which enters the plasma when they are destroyed. In addition to heparin, they are also able to bind to other natural anticoagulants.
- ***Other plasma coagulation and fibrinolysis*** factors (factors VII, IX, XI, XII) are also adsorbed on the surface of erythrocytes. By adsorbing thromboplastin on their surface, erythrocytes protect the body from intravascular clotting. In addition to the plasma factors mentioned earlier, erythrocytes contain a large amount of ADP, fibrinase, and other factors. They are also able to bind plasminogen and urokinase.

Considering the influence of erythrocyte factors on the stages of hemocoagulation, it is necessary to distinguish two groups of factors acting in different directions.

Erythrocyte factors that stimulate hemocoagulation **include:**

1. Thromboplastic factor
2. Anti-heparin factor
3. Ac-globulin.
4. Thrombin-like factor that promotes the conversion of fibrinogen to fibrin.
5. Fibrin-stabilizing factor.
6. АДФ.
7. Adsorption of heparin and heparin-like substances by erythrocytes and their delivery to the kidneys.
8. Erythrocytes uptake of urokinase and decreased fibrinolysis activity.

Erythrocyte factors that interfere with blood clotting**:**

1. Antithromboplastic factor.
2. Antithrombins.
3. Substances that help to dissolve a blood clot (e.g., erythrokinase). At the same time, if the formation of a blood clot is accompanied by hemolysis, then the released proactivator and plasminogen activator contribute to rapid blood thinning.

Leukocytes

Leukocytes, like other formed elements of blood, also contain clotting and fibrinolysis factors. In contrast to erythrocyte and platelet factors, leukocyte factors are not well understood. However, it is known that when stimulated by antigens, monocytes and macrophages synthesize ***apoprotein III,*** the protein part of thromboplastin, which significantly accelerates blood clotting. These same cells produce ***vitamin K-dependent clotting*** factorsAnd as is known, these factors play a significant role in the occurrence and development of **disseminated intravascular blood coagulation (DIC) in** many inflammatory and infectious diseases, which significantly aggravates the course of the pathological process, and sometimes serves as a direct cause of death in patients.

In addition to the previously mentioned factors**, *a thromboplastic*** factor resembling platelet factor 3 is detected in leukocytes. However, along with it, leukocytes produce a compound resembling tissue thromboplastin. These two compounds are actively involved in blood clotting processes in both normal and pathological conditions.

It has been proven that when a vessel is injured, not only platelets, but also leukocytes rush to the site of injury, which adhere (especially under the influence of ADP) to the wound surface,

thereby releasing a procoagulant that has the properties of a tissue thromboplastin. As a result of these processes, thrombin is rapidly formed, which induces platelet metamorphosis and the launch of a coagulation cascade of blood clotting, i.e. at the beginning of the injury, the formation of a fibrin clot is accelerated.

This leads to the fact that in a number of pathological conditions, a large amount of procoagulant is released from leukocytes and hypercoagulation develops, i.e. the first phase of DIC syndrome. In addition, it has been proven that leukocytes are also involved in the formation of fibrin thrombus: it has been established that a thrombus among fibrin strands contains a significant number of leukocytes (about 15 times more than in the same volume of blood). On the other hand, in the later stages of injury, they inhibit platelet adhesion, promoting blood movement and nourishment to the injured areas.

At the same time, leukocytes contain ***anti-heparin factor, antihemophilic globulin, as*** well as XII and other ***plasma factors.*** Hagemann factor is thought to be adsorbed from plasma. It is able to enhance hemocoagulation, as well as participate in the formation of fibrin-inflammatory exudates.

Leukocytes have **anticoagulant and fibrinolytic activity.** Anticoagulants are released during the breakdown of leukocytes, which occurs not only during pathological processes, but also under physiological conditions.

Granulocytes are known to keep the blood in a fluid state by secreting heparin, plasminogen, as well as proactivator and fibrinolysis activators. In addition, basophils contain heparin. It is these cells that are currently considered to be microreservoirs of heparin. In neutrophils, an anticoagulant of antithrombin and antithromboplastic action was detected.

Leukocytes play an important role in the regulation of fibrinolysis. They contain lytic enzymes (cathepsins) that convert plasminogen into plasmin and provide chemical thrombolysis. In addition, leukocytes are able to carry out mechanical thrombolysis by involving granulocytes in the blood clot as a result of amoebe-like movement, as well as phagocytic thrombolysis due to the capture of fibrin by neutrophils with its subsequent digestion.

The fibrinolytic activity of leukocytes under physiological conditions and in pathology may be associated with the presence of alkaline and acid phosphatases in them, which are capable of converting plasminogen into plasmin. These substances are found in lymphocytes, neutrophils, eosinophils, and monocytes.

The role of erythrocytes and leukocytes in the implementation of hemostasis is not limited to the above-mentioned processes, however, a deeper elucidation of their role in hemostasis is the subject of further scientific research.

Anti-coagulation system (SPS).

PSS is a set of physiological mechanisms aimed at preserving the fluid state of the blood, preventing hemocoagulation. PSS includes a range of substances called anticoagulants, which come in natural and artificial origins.

Anticoagulation mechanisms play a leading role in maintaining the fluid state of the blood and in limiting the process of thrombus formation. However, they have been studied much less than the process of blood coagulation, and therefore the issues of function and physiological regulation of the anticoagulation link of the hemostasis system remain largely debatable.

Artificial anticoagulants.

I. Direct action (directly disrupt blood clotting) 1. Sodium citrate Bind calcium 2. Sodium oxalate	II. Indirect Action (block the synthesis of coagulants in the liver) 1. dicumarin; 2. Swaddling.

Naturally occurring anticoagulants

I. Primary (present in the blood before clotting begins) 1. antithrombin III (α2-globulin) – inhibits thrombin, Xa, IXa, VIIa, XIIa, concentration 240 mg/ml; 2. Heparin is an immediate-acting anticoagulant, concentration 30-70 mg/l (activates 1.); 3. antitrypsin; 4. inhibitor of C, a component of complement; 5. Prostacyclin (synthesized by the endothelium from arachidonic acid) inhibits platelet aggregation.	II. Secondary (formed during blood clotting and fibrinolysis) 1. antithrombin I (fibrin) – adsorbs and inactivates thrombin; 2. fibrin degradation products – increase fibrin monomer polymerization, inhibit platelet aggregation; 3. protein "C" – inactivates factors V, VIII; 4. Protein "S" – reduces the ability of thrombin to activate clotting factors.

The endothelium plays an important role in hemostasis, which is due to a number of factors.

First, the normal endothelium has a smooth surface provided by a layer of glycocalyx covering it from the inside. Glycocalyx consists of glycoproteins that have anti-adhesive properties, that is, they prevent platelets from sticking to the endothelium.

Secondly, the charge of the vessel wall is positive, which also prevents platelets with a positive charge from approaching the endothelium.

Third, the endothelium can produce coagulation factors (vasoconstrictors) and anticoagulation factors (vasodilators).

Fourth, the endothelium adsorbs numerous anticoagulant substances from blood plasma. As long as the endothelium is intact and intact, it synthesizes mainly anticoagulation factors, which are also vasodilators.

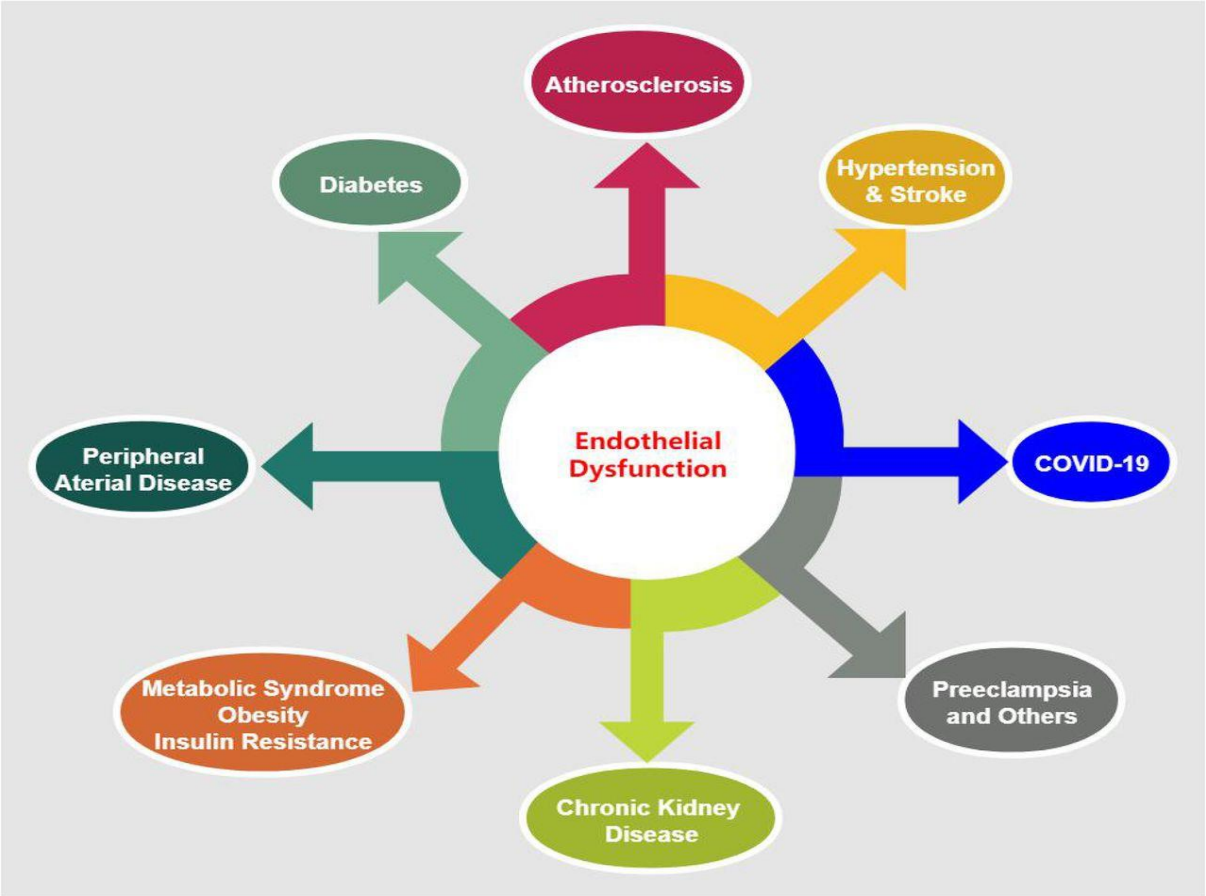


Fig.17 Coagulation factors and endothelial fibrinolysis

Main endothelial-produced anticoagulants

As long as the endothelium is intact and intact, it synthesizes mainly anticoagulation factors, which are also vasodilators.

Nitric oxide

Nitric oxide (NO) is the most important molecule that regulates vascular homeostasis and maintains normal basal tone of blood vessels, normalizing their reactivity, ability to dilatation, and blood pressure level. With anti-aggregation and anti-adhesive properties, nitric oxide has an antithrombotic effect.

Prostacyclin

Prostacyclin (prostaglandin PgI2) is formed from phospholipids. Acting on the smooth muscle membrane, prostacyclin activates adenylate cyclase, which increases the content of cAMP in the

cell, which reduces the level of Ca2+ in them. Thus, prostacyclin acts as an antiplatelet factor, an anticoagulant factor, and the mechanism of action is the same as that of nitric oxide: the removal of calcium ions from smooth muscle, which prevents vasospasm, platelet aggregation and blood clotting. Prostacyclin and Nitric oxide normalizes lipid metabolism, prevents the development of atherosclerosis, and inhibits the growth process.

Thrombomodulin

The vascular endothelium synthesizes a single-chain glycoprotein - **thrombomodulin, which performs the function of a thrombin receptor. Thrombin, having joined to thrombomodulin, acquires new properties: together with anticoagulant proteins** C and S, it forms an antiplatelet and antithrombotic complex, which prevents coagulation and inhibits fibrinolysis. Thus, the vascular endothelium, through the thrombomodulin receptor, blocks **The most active clotting factor is thrombin**.

Antithrombin III

In addition to the endothelium, antithrombin III is also produced in the liver. It is a very strong activator of heparin, which is adsorbed by the endothelium from the blood. Heparin is formed in the liver, lungs, basophils, and mast cells. The endothelium itself synthesizes heparin-like substances (chondroitin sulfates, hyaluronic acid, heparitin)

Thus, under normal physiological conditions, the vascular endothelium prevents adhesion and aggregation of platelets, blood coagulation and vasospasm, synthesizing a group of active substances: nitric oxide, prostacyclin, antithrombin III, etc. Finally, the endothelium adsorbs anticoagulants from the blood plasma, inhibiting the adhesion and aggregation of platelets on its surface (heparin, proteins C and S).

Main procoagulants produced by the endothelium

After stimulation or injury, the endothelium transforms into a powerful procoagulant surface. This is due to the synthesis, isolation or attraction of many procoagulant substances.

Tissue thromboplastin

Tissue thromboplastin is a high-molecular lipoprotein found in various tissues (brain, liver, kidneys, lungs, etc.) and vessels (mainly in endothelial cells), from where it is released during injuries. It is involved in the formation of prothrombinase, which contributes to the rapid formation of a fibrin clot.

Endothelins

Endothelins are bicyclic polypeptides consisting of 21 amino acid residues with two bisulfide bonds. There is a great similarity between the structure of endothelins and some neurotoxic

peptides (venoms of a burrowing scorpion). The main mechanism of action of endothelins is the release of calcium, which causes:

- stimulation of all phases of hemostasis, from platelet aggregation to the formation of a red thrombus;
- Contraction and growth of vascular smooth muscles, leading to thickening of the vessel wall and a decrease in their diameter - vasoconstriction.

Endothelin synthesis is enhanced by thrombin and platelets. Endothelins, in turn, induce platelet adhesion and aggregation.

Fibrinolysis inhibitors

Fibrinolysis inhibitors are found in the human aorta and other vessels, and in the lungs. They refer to antiplasmins, antiactivators, and plasminogen activation inhibitors.

Fibronectin

Fibronectin is a glycoprotein consisting of two chains connected by disulfide bonds. It is produced by all cells of the vascular wall, platelets. Fibronectin is a receptor for fibrin-stabilizing factor. Promotes platelet adhesion by participating in the formation of a white thrombus; binds heparin. By attaching to fibrin, fibronectin thickens the thrombus. Under the influence of fibronectin, smooth muscle cells, epithelial cells, and fibroblasts increase their sensitivity to factors growth, which can cause thickening of the muscular wall of the vessels (narrowing of the diameter).

The von Willebrand Factor

Von Willebrand factor is synthesized in endothelium and megakaryocytes. It is a sulfated glycoprotein with a large molecular weight; stimulates the onset of thrombus formation: promotes the attachment of platelet receptors to vascular collagen and fibronectin, as well as to each other, that is, enhances platelet adhesion and aggregation. The synthesis and release of von Willebrand factor increases under the influence of vasopressin, when the endothelium is damaged. As all stressor conditions increase the secretion vasopressin, then under stress, extreme conditions, the thrombogenicity of blood vessels increases, which is facilitated by an increase in the synthesis of von Willebrand factor. In addition, von Willebrand factor stabilizes the factor VIII molecule by increasing its half-life and transporting it to sites of active hemostatic plug formation.

Thrombospondin

Thrombospondin is a glycoprotein that is produced by the vascular endothelium, but is also found in platelets. It forms complexes with collagen, heparin, is a strong aggregating factor, mediating the adhesion of platelets to the subendothelium.

Thus, in a physiological state, the endothelium creates conditions for adequate local blood flow, synthesizing powerful anticoagulants, which are also vasodilators. The activity of the endothelium normally ensures the trophism of organs and performs a protective function due to the presence of highly organized self-regulation mechanisms in the endothelium. When the function or structure of the endothelium is disturbed, the spectrum of biologically active substances secreted by it changes dramatically. The endothelium begins to secrete aggregants, coagulants, and vasoconstrictors. Under unfavorable conditions (hypoxia, metabolic disorders, atherosclerosis, etc.), the endothelium becomes the initiator of many pathological processes in the body.

The Role of Endothelial Function

When blood vessels are damaged, the endothelium loses its negative charge and changes it to a positive one. Negatively charged platelets adhere to the positively charged wound surface (adhesion).

Adhesion factors: excess positive charge at the site of injury; capillary subendothelial collagen – platelet activation factor; the Hagemann factor (XII); von Willebrand factor; Fibropectin is a factor in platelet spreading on the vascular wall.

1) reversible aggregation (crowding, gluing of platelets to form conglomerates of 10-20 platelets). When the platelet sticks to the injury site, they change their charge from negative to positive, and a new portion of platelets is attracted to them, which leads to the formation of a platelet aggregate. But this process is reversible, i.e. mechanical impact or an increase in blood pressure can lead to the breakdown of platelet tests

2 Irreversible aggregation. When platelets are activated, actin and myosin filaments contract, which leads to degranulation of platelets, the contents of the granules seem to glue the platelets into one whole.

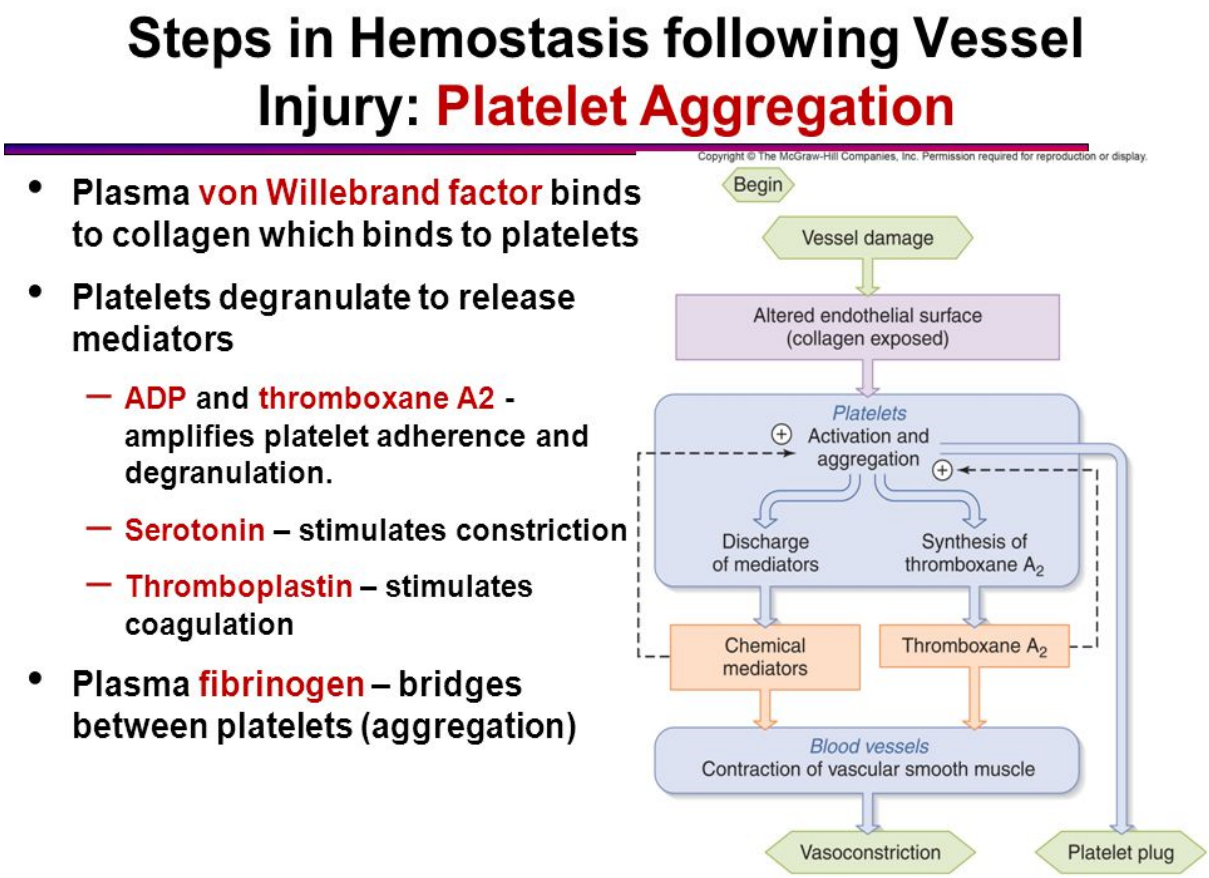


Fig.18. Steps in Hemostasis following Vessel Injury: Platelet Aggregation

Blood coagulation (hemocoagulation, coagulation, part of hemostasis) is a complex biological process of the formation of fibrin protein filaments in the blood, forming blood clots, as a result of which the blood loses fluidity, acquiring a curd-like consistency.

Coagulation is the process of blood clotting. When the vessel wall is destroyed, platelets gather at the site of injury and secrete thromboplastin, which, along with calcium, vitamin K and prothrombin, contributes to the conversion of fibrinogen into fibrin. Fibrin networks are formed, where the formed elements of the blood are retained. This is a blood clot called a thrombus. The coagulation process lasts 3-8 minutes.

In a healthy person, bleeding from small vessels stops in a few minutes (the so-called "bleeding time"). This primary hemostasis is almost entirely due to vasoconstriction and mechanical blockage by platelet aggregates.

The process of hemostasis is reduced to the formation of a platelet thrombus. Conventionally, it is divided into three stages:

temporary (primary) vasospasm;

formation of a platelet plug due to adhesion and aggregation of platelets;

retraction (contraction and hardening) of the platelet plug.

Vascular damage is accompanied by immediate platelet activation. The adhesion of platelets to connective tissue fibers at the edges of the wound is caused by the glycoprotein von Willebrand factor.

Simultaneously with adhesion, platelet aggregation occurs with the help of fibrinogen, a protein found in plasma and platelets. With its help, connecting "bridges" are formed between platelets, which leads to the appearance of a platelet plug.

Platelets that have undergone adhesion and aggregation are intensively secreted with various biologically active substances (ADP, adrenaline, norepinephrine, etc.), which lead to secondary, irreversible aggregation. Simultaneously with the release of platelet factors, thrombin is formed, which acts on fibrinogen to form a fibrin network in which individual red blood cells and leukocytes get stuck.

Thanks to the contractile protein thrombostenin, platelets are pulled to each other, the platelet plug contracts and thickens, and its retraction occurs[

BLOOD CLOTTING PROCESS

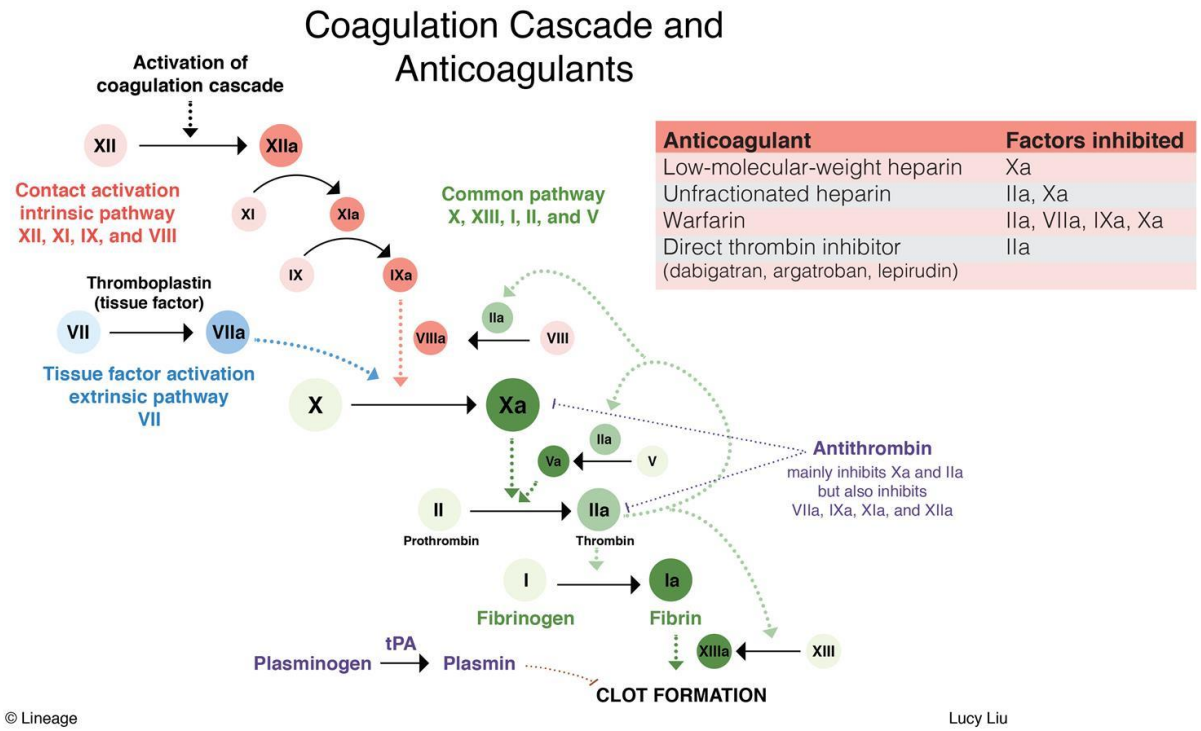


Fig.19. Diagram of interaction of blood coagulation factors

The process of blood coagulation is predominantly a proenzyme-enzyme cascade, in which proenzymes, passing into an active state, acquire the ability to activate other blood clotting factors.

In its simplest form, the blood clotting process can be divided into three phases:

The activation phase includes a set of sequential reactions leading to the formation of prothrombinase and the transition of prothrombin to thrombin

The coagulation phase is the formation of fibrin from fibrinogen

The retraction phase is the formation of a dense fibrin clot

Due to the destruction of tissue cells and the activation of platelets, phospholipoprotein proteins are released, which, together with plasma factors Xa and Va, as well as Ca2+ ions, form an enzyme complex that activates prothrombin. If the clotting process is started by phospholipoproteins secreted from the cells of damaged vessels or connective tissue, we are talking about an external blood clotting system; If the initiation occurs under the influence of coagulation factors present in the plasma, the term internal coagulation system is used. Both systems complement each other.

In the process of adhesion, the shape of platelets changes – they become rounded cells with spiny processes. Under the influence of ADP (partially released from damaged cells) and adrenaline, the ability of platelets to aggregate increases. At the same time, serotonin, catecholamines and a number of other substances are released from them. Under their influence, the lumen of the damaged vessels narrows, and functional ischemia occurs. Eventually, the vessels are blocked by a mass of platelets stuck to the edges of the collagen fibers at the edges of the wound.

At this stage of hemostasis, thrombin is formed under the action of tissue thromboplastin. It initiates irreversible platelet aggregation. By reacting with specific receptors in the platelet membrane, thrombin induces the phosphorylation of intracellular proteins and the release of Ca2+ ions.

Normally, blood is a fluid that has a viscosity close to that of water. There are many substances dissolved in the blood, of which the protein fibrinogen, prothrombin and calcium ions are the most important in the clotting process. The process of blood clotting is carried out by a multi-step interaction on phospholipid membranes ("matrices") of plasma proteins called "clotting factors" (clotting factors are denoted by Roman numerals; if they become activated, the letter "a" is added to the factor number). These factors include proenzymes that are converted into proteolytic enzymes after activation; proteins that do not have enzymatic properties, but are necessary for fixation on membranes and the interaction of enzyme factors (factors VIII and V) with each other.

After the walls of blood vessels are damaged, tissue thromboplastin enters the blood, which triggers the blood clotting mechanism, activating factor XII.

In the presence of calcium ions in the blood, the polymerization of soluble fibrinogen and the formation of a structureless network of insoluble fibrin fibers occurs. From this moment on, the formed elements of the blood begin to be filtered in these threads, creating additional rigidity to the entire system, and after a while forming a thrombus that clogs the site of the rupture, on the one hand, preventing blood loss, and on the other hand, blocking the entry of external substances and microorganisms into the blood.

Blood clotting is affected by many conditions. For example, cations speed up the process, while anions slow it down. In addition, there are substances that completely block blood clotting (heparin, hirudin, etc.) and activate it (gyurza poison, feracrylic).

Congenital disorders of the blood clotting system are called hemophilia.

Depending on the triggering mechanisms, there are external and internal blood clotting pathways. In both the external and internal pathways, the activation of coagulation factors occurs on the membranes of damaged cells.

Platelet coagulation factors and fibrinolysis

Platelet coagulation factors are usually divided into endogenous (formed in the platelets themselves) and exogenous (plasma factors adsorbed on the surface of platelets).

Platelet coagulation factors and fibrinolysis are components of the platelet link of hemostasis.Endogenous platelet factors are usually denoted by Arabic numerals, in contrast to plasma factors, which are denoted by Roman numerals. It should be noted that of the platelet factors described below, five correspond to the generally accepted nomenclature, the numbering of the remaining factors is conditional and may not correspond to that in other literature. Most studied 12 endogenous platelet factors.

Endogenous platelet factors

Platelet factor 1 is involved in the formation of prothrombinase and accelerates the formation of thrombin from prothrombin, similar to plasma factor V. It is in an inactive state. Traces of thrombin are needed to make it active.

Platelet factor 2 – **thrombin accelerator**, **fibrinoplastic factor** – accelerates the conversion of fibrinogen to fibrin.

Platelet factor 3 – platelet thromboplastin**, membrane phospholipid** factor – is a lipoprotein. It serves as a matrix **for the interaction of plasma hemocoagulation factors** and the formation of their active complexes. In terms of its properties, this factor is identical to cephalin and erythrocyte membrane factor – erythrocytin, erythrophosphatide. It is necessary for the endogenous formation of prothrombinase, which promotes the conversion of prothrombin to thrombin. Factor 3 is released by platelet aggregation.

Platelet factor 4 – antiheparin **– has a pronounced anti-heparin activity, neutralizing the heparin activity of plasma. The release of factor 4 from platelets is facilitated by thrombin, and partly by Hagemann factor. A decrease in platelet count increases the sensitivity of the blood to heparin.**

Platelet factor 5 is agglutinatable**, or** clotting**, similar in its properties** to plasma fibrinogen. It is intensively excreted from platelets under the influence of thrombin. Platelet factor 5 is involved in platelet aggregation and thus contributes to the creation of a strong thrombus.

Platelet factor 6 is **antifibrinolytic.** Delays fibrinolysis.

Platelet factor 7 is antithromboplastic**. It prevents the formation of active prothrombinase, and also slows down the conversion of prothrombin to thrombin. In the presence of heparin, its anticoagulant effect is enhanced.**

Platelet factor 8 – **retractozyme**. It is a contractile protein of platelets called thrombostenin, which resembles the actomyosin of muscle fibers. When thrombosthenin shrinks, the blood clot retractions. At the same time, platelets are pulled towards each other, which in turn leads to the convergence of fibrin filaments. The clot becomes dehydrated and more compact.

Platelet factor 9 is serotonin, or vasoconstrictor factor. Platelets are enriched with serotonin as they pass through the vessels of the gastrointestinal tract and liver. Serotonin is released from platelets during their aggregation caused by ADP, adrenaline, collagen. Serotonin has many properties: it has a vasoconstrictor effect, changes blood pressure, is a heparin antagonist; in thrombocytopenia It is able to normalize the retraction of a blood clot and, in the presence of thrombin, accelerate the transition of fibrinogen to fibrin. Serotonin plays an important role in the course of allergic reactions, in the activity of the central nervous system, heart and blood vessels, the musculoskeletal system and in the development of infectious diseases.

Platelet factor 10 is a lamellar cofactor**, cothromboplastin,** or activator of the thromboplastin found in snake venom. Cothromboplastin **is** able to accelerate the transition of prothrombin to thrombin not only in combination with snake venom, but also in the presence of pulmonary tissue thromboplastin, **plasma factor V** and Ca2+. The role of cothromboplastin in the blood clotting process under normal conditions is not clear.

Platelet factor 11 is a fibrin-stabilizing factor , a substance similar **to plasma factor XIII**. It is involved in the stabilization of fibrin (conversion of soluble fibrin into insoluble fibrin).

Platelet factor 12 – ADP (adenosine diphosphate) **– is a** platelet aggregation factor. When platelets come to the surface, ADP promotes their adhesion to each other. In addition, ADP enhances the adhesion of platelets to the damaged vessel wall.

Exogenous platelet factors

Various plasma factors of blood coagulation and fibrinolysis can be adsorbed on the surface of platelets – prothrombin, thromboplastin, proaccelerin, convertin, factors VIII, IX, X, XI, XII, plasminogen and others. They form the so-called plasma atmosphere of platelets, which plays a role in the thickening and consolidation of the lamellar thrombus.

Erythrocyte coagulation factors and fibrinolysis

Erythrocytes, as well as platelets, play a role in **hemostasis**. However, erythrocyte clotting factors and fibrinolysis are not yet well understood. It has been found out that some of these factors are intraerythrocyte, that is, they belong to a certain structure of the erythrocyte, while others are extra-erythrocyte, that is, they are plasma coagulation and fibrinolysis factors adsorbed on the surface of the erythrocyte, as well as plasma anticoagulants.

Intraerythrocyte factors

Erythrocyte thromboplastic factor (**erythrocytin**) is a substance with thromboplastic activity that affects the blood clotting process regardless of the presence of tissue thromboplastin and platelets. It has the properties of a platelet factor of 3.

The ability of red blood cells to release erythrocytin into plasma is influenced by mediators and hormones such as adrenaline, norepinephrine, acetylcholine, histamine and thrombin. This is due to the effect of these substances on the permeability to ions of the erythrocyte membrane, on the osmotic resistance of erythrocytes, on the decrease in their electrophoretic mobility, which is due to a decrease in the negative electrokinetic charge.

Erythrocytin participates in the formation of prothrombinase in the endogenous mechanism of blood coagulation, being an endogenous factor of erythrocytes.

Erythrocyte antiheparin factor. Both destroyed and intact erythrocytes have antiheparin activity. It is possible that erythrocyte antiheparin factor is able to be released into the plasma.

Erythrocyte accelel is a compound similar to plasma factor V.

Erythrocyte thrombin-like factor, a compound resembling platelet factor 2, promotes the conversion of fibrinogen to fibrin.

Erythrocyte fibrinogen. The erythrocyte adsorbs plasma fibrinogen on its surface in significant quantities. The negative charge of red blood cells plays an important role in the binding of fibrinogen, although fibrinogen itself carries a negative charge. It is assumed that adsorption occurs due to regions of the fibrinogen molecule with positively charged prosthetic groups. This mechanism is able to regulate the concentration of fibrinogen in the blood.

Fibrinogen plays an important role in the mechanism of red blood cell aggregation. In addition, fibrinogen adsorbed on the surface of erythrocytes coagulates as a result of thrombin, as a result of which erythrocytes are firmly fixed between fibrin strands.

Erythrocyte fibrin-stabilizing factor contributes to the formation of dense stabilized fibrin insoluble in 5M urea solution. It is found in hemolysed and, to a lesser extent, intact red blood cells.

ADP is an erythrocyte factor that enhances the adhesion and aggregation of platelets. Destroyed erythrocytes have a stronger effect on the adhesive-aggregation activity of platelets than intact ones.

Erythromboplastic factor is an anticoagulant found in red blood cell hemolysate. Such hemolysate dramatically slows down and sometimes completely prevents blood clotting. The presence of heparin in plasma does not affect the antithromboplastic activity of erythrocytes.

Erythrocyte antithrombins. Erythrocytes are able to adsorb heparin on their surface, which, when destroyed, enters the plasma.

Erythrocyte factors that affect blood clot retraction. They are contractile proteins in erythrocytes, resembling the actomyosin of muscle fibers.

Erythrocyte fibrinolysis factors. They are fibrinolysis activators, which are partly found inside red blood cells and partly adsorbed from plasma. Plasminogen proactivators were found in hemolysate and stroma.

Fibrinolysis inhibitors neutralize plasminogen proactivators and activators, plasmin itself.

Fibrinolysis activators and inhibitors in red blood cells play an important role in the process of dissolving a blood clot. Destroyed erythrocytes mainly stimulate fibrinolysis, while intact erythrocytes inhibit this process.

Extra-erythrocyte factors

Other plasma factors of blood coagulation and fibrinolysis are also adsorbed on the surface of erythrocytes: factors VII, IX, XI, XII. By adsorbing thromboplastin on their surface, erythrocytes protect the body from the formation of blood clots inside the vessels. Erythrocytes also bind natural anticoagulants, plasminogen and urokinase.

Leukocytes

Leukocyte anticoagulants include heparin, which is found in basophilic granulocytes, as well as an antithromboplastic anticoagulant found in neutrophils.

Leukocyte factors of fibrinolysis

Leukocytes contain lytic enzymes (cathepsins) that convert plasminogen into plasmin and carry out chemical thrombolysis. In addition, leukocytes contribute to the dissolution of the thrombus by mechanical thrombolysis (involvement of granulocytes in the blood clot as a result of amoeboid movement) and phagocytic thrombolysis (part of the fibrin is captured by neutrophils and further digested).

Plasminogen, plasmin, and plasminogen proactivators were found in granulocytes. Fibrinolysis inhibitors such as antiplasmin and plasminogen activation inhibitors were also found in leukocytes.

The fibrinolytic activity of leukocytes in normal and pathological conditions may also be associated with the presence of acidic and alkaline phosphatases in them, which are able to convert plasminogen into plasmin. These substances are found in monocytes, eosinophils, neutrophils, and lymphocytes.

Of the plasma coagulation factors, fibrinogen (factor I), prothrombin (factor II), as well as factors V, VII, VIII, IX were found on leukocytes.

Plasma anticoagulants

Plasma anticoagulants can be divided into two large groups: physiological, determined in the blood under normal (natural) conditions, and pathological, appearing in the blood in a number of pathologies. Physiological anticoagulants, in turn, are divided into primary (independently synthesized in the body) and secondary (formed in the process of blood clotting, fibrinolysis and activation of other proteolytic systems).

The role of plasma anticoagulants in the hemostasis system is that they limit thrombus formation and thereby contribute to the preservation of the fluid state of the blood.

Primary physiological anticoagulants

Antithrombin III is an alpha2-glycoprotein synthesized in the liver. It is also called **heparin cofactor I**. Antithrombin III inactivates thrombin and other activated coagulation factors – XIIa, XIa, Xa, IXa, plasmin and kallikrein. Antithrombin III, like other physiological anticoagulants, has no effect on non-activated coagulation factors. Antithrombin III accounts for more than 75% of all plasma anticoagulant activity.

Heparin is a sulfated polysaccharide synthesized in mast cells and is found in large quantities in the liver and lungs. It is a cofactor of antithrombin III - it converts the latter into an anticoagulant of immediate action. With Fibrinogen, Factor XIII, Plasminogen, Plasmin, Antiplasmin, adrenaline, thyroxine, serotonin forms complexes with anticoagulant and fibrinolytic properties. In low concentrations, it inhibits the reaction between plasma factors

IXa, VIII and platelet factor 3, autocatalytic activation of thrombin, and the action of plasma factor Xa. In high concentrations, it inhibits the blood coagulation process in all phases. It inhibits some platelet functions, including the release of serotonin.

Protein C is a K-vitamin-dependent protein synthesized by hepatocytes. It circulates in the blood in an inactive form. Protein C is activated by a small amount of thrombin. This reaction is significantly accelerated by thrombomodulin , a surface protein in endothelial cells that binds to thrombin. Thrombin in complex with thrombomodulin acquires anticoagulant properties and activates protein C.

It is also activated by factor X, trypsin and Russell's viper venom. Inactivates factors VIII and V. Activated protein C inhibits the production of plasminogen activator inhibitor by endothelial cells through a feedback mechanism. This indirectly stimulates the fibrinolytic system and enhances the anticoagulant activity of activated protein C.

Protein S is a vitamin-dependent protein synthesized by hepatocytes and endothelial cells. It is a cofactor of protein C. It dramatically weakens the ability of thrombin to activate factors VIII and V, and enhances its activating effect on protein C.

Alpha2-macroglobulin is a glycoprotein that slowly inhibits thrombin, kallikrein, plasmin and trypsin. It has the ability to bind the activated components of blood coagulation and fibrinolysis and turn them off from interaction with other factors.

A contact inhibitor is a specific inhibitor of factor XIa.

Antithromboplastins are inhibitors of the factor III-factor VIIa complex.

Complement-I inhibitor – inhibits factors XIa, XIIa, kallikrein.

Alpha1-antitrypsin – inactivates factors XIa, IIa and plasmin.

Lipid inhibitor, or **anticephalin**, competitively inhibits platelet factor 3, erythrocytin, kephalin, disrupts the internal and external mechanisms of prothrombin formation.

Fibrin monomer polymerization inhibitor – inhibits fibrin self-assembly.

Secondary physiological anticoagulants

Secondary physiological anticoagulants are formed in the process of blood coagulation and fibrinolysis as a result of further enzymatic degradation of a number of coagulation factors, as a result of which, after initial activation, they lose the ability to participate in the hemocoagulation process and acquire the properties of anticoagulants.

Fibrin, or **antithrombin I**, adsorbs and inactivates large amounts of thrombin.

Antithrombin IX is a product of the breakdown of prothrombin by thrombin. It interferes with the activation of prothrombin and prothrombinase.

Auto-II-anticoagulant is a product of thrombin cleavage of protein C. Competitively inhibits factor Xa; by blocking antiplasmins, it increases fibrinolysis; it is a cofactor of epinephrine aggregation of platelets.

Antithromboplastins are waste products of factor VII or X activation, which inhibit the action of tissue thromboplastin or its complex with factor VII.

Metafactor Va is an inhibitor of factor Xa.

Metafactor XIa is an inhibitor of the XIIa-XIa factor complex.

Fibrinopeptides are products of fibrinogen proteolysis by thrombin. They have anti-IIa properties.

Fibrin degradation products (PDFs) are products of fibrin cleavage by plasmin. They disrupt the polymerization of fibrin monomers, block fibrinogen, inhibit factor IXa, fibrinolysis and platelet aggregation, and have a weak anti-IIa effect.

Pathological anticoagulants

In certain types of pathology, very powerful immune inhibitors of blood clotting, which are specific antibodies against a particular factor, can accumulate in the plasma. Such antibodies can be produced against any clotting factors, but factor VIII and IX inhibitors are the most common in the clinic.

In addition, in a number of autoimmune processes and paraproteinemias, pathological proteins can accumulate in the blood that have either an antithrombin effect or an inhibitory effect on factors Xa, II, or V.

Examination of the plasma hemostasis system

1) Determination of blood clotting time

There are several methods for determining the clotting time:— Bürker's method: by estimating

the time of appearance of fibrin filaments in a drop of whole blood on a watch glass when stirred with a glass stick. The norm is from 2.5 minutes to 5.5 minutes.— the Lee-White method by estimating the time of spontaneous blood coagulation at a temperature of 37 °C. The norm is 6-10 minutes.

Method for determining blood coagulation time according to Mas-Magro.

A large drop of petroleum jelly is poured onto a watch glass covered with a thin layer of paraffin. A needle or disposable lancets is injected into the flesh of a finger thoroughly cleaned with alcohol. Wipe off the protruding drop of blood, carefully squeeze out a new drop and suck it into a pipette from a Sali hemometer (20 mm3), previously moistened from the inside with paraffin oil. Blood from the pipette is immediately blown into a drop of oil on the watch glass, this moment is marked on the watch as the beginning of the study. Every minute, the blood is sucked back into the pipette by wiping the tip of the pipette with filter paper. As long as the blood has not clotted, it rises into the pipette; When clotting occurs, it becomes impossible to pump it. Normally, human blood at t° 25° coagulates in 8 to 12 min. Blood coagulation is determined by this method at t° 15 to 25°.

Interpretation:

1) Prolongation of blood coagulation time is observed in coagulopathies (deficiency of one of the factors of the plasma coagulation system: factors XII, XI, IX, VIII). Shortening of clotting time indicates a tendency towards hypercoagulability.2) Determination of plasma recalcification time due to the newly acquired plasma clotting capacity when calcium chloride solution is added to the plasma. Normally, the time of clot formation is 90-150 seconds.

Interpretation:

A prolongation of the plasma recalcification time of more than 250 seconds is considered pathological, which indicates the presence of coagulopathy in the patient, while a shortening of the plasma recalcification time indicates a tendency to hypercoagulation.

3) Determination of prothrombin intake due to the absence of prothrombin intake in impaired blood thromboplastin formation. Normally, the time of prothrombin consumption is 30-60 seconds.

Interpretation:

Shortened prothrombin clotting time may be due to a deficiency of one of the plasma proteins involved in thromboplastin formation or a deficiency of platelet factor 3. The addition of the missing factor to the plasma corrects the thromboplastination defect.4) Determination of the prothrombin index (PTI). Fluctuations of 80-100% are considered normal

Interpretation: A decrease in PTI values indicates a decrease in plasma coagulation properties, liver disease, anticoagulant use, and an increase may occur in thromboembolic conditions.

5) Determination of plasma fibrinogen concentration by converting fibrinogen to fibrin, followed by drying and weighing the clot. The norm is 2-3 g/l (200-300 mg%).

Interpretation:

Bleeding occurs when fibrinogen levels are below 60 mg% (0.6 g/L).6) Thrombus selastomography records the onset of clotting and changes in the elasticity of the blood clot over time.

Interpretation: **The** method allows to determine the formation, retraction and lysis of a blood clot. Assessment of coagulation activity is carried out according to the following main indicators:

R is the retraction time, which corresponds to the beginning of the coagulation process, i.e. the loss of the first fibrin filaments, reflects the rate of thromboplastin appearance. The norm is 8-10 minutes. The R constant increases when thromboplastin is deficient.

K is the coagulation time, which characterizes the rate at which fibrin filaments are formed by the interaction of fibrinogen with thrombin. The norm is 6-8 minutes. The K constant depends on the amount of fibrinogen and thrombin: in case of deficiency it lengthens, in case of excess it decreases.

Ma is the maximum amplitude, which characterizes the maximum elasticity of the formed clot. The norm is 45-60 mm. The value of Ma corresponds to the end of the productive coagulation phase, after which the retraction of the clot of m fibrinol begins, reflecting the coagulation activity of platelets and fibrinogen. A sharp prolongation of R and K in normal Ma is characteristic of hemophilia and anticoagulant use reflects increased fibrinolysis.

Examination of the platelet hemostasis system

Platelets belong to the third group of blood cell elements, have antigenic properties, their main role is participation in hemostasis.The number of platelets in healthy people is 180-320x10 9/l.

Interpretation:

A decrease in the number of platelets in the blood is an important symptom in some forms of hemorrhagic diathesis. Thrombocytopenia (50 x 10 9/L and below) is seen with exacerbation of thrombocytopenic purpura. Moderate thrombocytopenia (100x109/L) is observed in collagenosis, cirrhosis of the liver. Thrombocytosis is characteristic of myeloproliferative diseases and is observed in malignant neoplasms. High thrombocytosis (1000 x 10 9/L) may occur in patients after In clinical practice, the most common studies are the aggregation, adhesive properties of platelets.

Platelet adhesion is normally in the range of 20-55%.

Interpretation:

A decrease in the platelet retention index (adhesiveness) up to 0% is observed in a number of congenital thrombocytopathies and in von Willebrand disease.Platelet aggregationNormal values are 10-60 s.

Interpretation:

In Glanzmann thrombasthenia, platelet aggregation does not occur. When examining patients with congenital bleeding of microcirculatory and microcirculatory-hematoma types, the differential diagnostic value of combinations of aggregation disorders when using a set of stimulants should be taken into account.

Interpretation: A decrease in blood clot retraction is observed in severe thrombocytopenia and thrombasthenia (up to complete absence—-0).

Fibrinolysis Study

Anticoagulant mechanisms are represented by two groups of anticoagulants: physiological, which are formed independently of blood coagulation and fibrinolysis, and anticoagulants, which are formed in the process of blood coagulation and fibrinolysis. The former include antithrombokinases (antithromboplastins), antithrombins, heparin, etc. All of them have an inhibitory effect on various phases of the blood coagulation process. Antithrombokinases inhibit the initial phase of blood coagulation and inhibit the activity of the formed thrombokinase. Antithrombins slow down the conversion of prothrombin to thrombin and prevent thrombin from acting on fibrinogen. Heparin disrupts the formation of thrombokinases, inactivates thrombin, binds fibrinogen, i.e. inhibits all phases of the coagulation process. The second group of anticoagulants includes substances that are formed as a result of blood coagulation and fibrinolysis and have an anicoagulant effect. Inhibitory mechanisms exist at every phase of blood clotting. The normal vascular endothelium plays a role in preventing platelets and coagulation contact factors from entering the coagulation process.

For the preparation of defibrinated blood, the most commonly used salt is tricalic, dikalic salt of ethylenediaminetetraacetic acid (EDTA), trisodium citrate and heparin. The first two substances inhibit coagulation by removing calcium from the blood.

Of the known anticoagulants of the 1st phase of coagulation, the most physiologically important are the inhibitor of activated factor XI (XIa), which belongs to α-2-globulins, and antithromboplastins (inhibitors of the factor III-factor VIIa complex). Inhibitors of the 2nd phase of coagulation include antithrombin II – α-2-γlobulin in the blood; inhibits not only thrombin, but also other activated coagulation factors – Ha, IXa, XIa, XIIa, kallikrein. Antithrombin III accounts for most of the spontaneous anticoagulant activity, which determines its leading role in maintaining a fluid state of the blood and preventing thrombosis. The share of other natural antithrombins, α-2-macroglobulin and α-1-antitrypsin, accounts for only about 25% of the anticoagulant activity of defibrinated blood plasma. The conversion of plasminogen into the active form occurs with the help of activators that are found in blood plasma, urine, and various tissues; formed in the vascular endothelium. The activator (urokinase) found in the urine is produced by the kidney. Under the influence of activators, the enzymatic cleavage of the plasminogen molecule occurs and plasmin is formed, which has a pronounced proteolytic property in relation to fibrin-fibrinogen (in addition, factors VII, V, complement, and some hormones). Fibrinogen lysis occurs in several stages. First, after the separation of small fragments A, B, and C, a high-molecular X-fraction is formed. It is then split into D and Y fractions. Subsequently, the Y fraction is split into a second D fraction and an additional E fraction. The D and E fractions are the end products of fibrinogen degradation. Plasmin

degradation of soluble fibrin is similar to that of fibrinogen, except that small fragments are absent in the first step. The degradation of stabilized fibrin is distinguished by the formation of a double-sized D-dimer fragment instead of the D fraction.

Enzymatic fibrinolysis is supported by complex compounds of heparin with fibrinogen, epinephrine, urea, plasmogen, which have the ability to lyse unstabilized fibrin clots (non-enzymatic fibrinolysis). Fibrin can be lysed by proteases secreted by leukocytes, which also participate in fibrinolysis due to the release of leukocyte plasminogen activators and phagocytosis of fibrin cleavage products. Kowalski's method (precipitation in an acidic environment and at low temperature of the euglobulin fraction containing coagulation factors and fibrinolysis, mainly plasminogen). 0.1 ml of oxalate plasma (1:9) is placed in a centrifuge tube, 1.8 ml of acidic water (pH 5.2) is added, the tube is placed in the refrigerator at 4 °C (in this case, the euglobulin fraction falls out of the plasma). After 30 minutes, the tube is removed and centrifuged for 10 minutes at 2000 rpm. The supernatant is sucked out, 0.1 ml of sodium borate is added to the sediment and placed in a thermostat at 37 °C for several minutes until the sediment is completely dissolved. Add 0.1 ml of calcium chloride solution (fibrinogen contained in the euglobin fraction is converted into fibrin). The time of clot formation is timed and the tube is placed in the thermostat until the clot is completely lysed. The time from the moment of clot formation to its dissolution expresses the fibrinolytic activity of the blood, which is normally equal to 3-4 hours. Methods for studying fibrinolysis based on additional standardized activation by streptokinase are used, as well as methods for detecting fibrinolysis products in blood plasma, such as PDF (immunological and chemical) and their compounds with fibrin monomers and fibrinogen (paracoagulation tests), methods for studying non-enzymatic fibrinolysis according to B.A. Kudryashov [13,14,15].

CHANGES IN HEMOSTASIS AND FIBRINOLYSIS IN DISEASES

The rheological bases of macrocirculation and microcirculation are inextricably linked with the hemostasis system or generally represent a single whole. In recent years, the main direction in the study of the mechanism of thrombosis has been the study of the role and function of platelets, interaction with the vascular wall, assessment of the initial stages of coagulation and the role of intermediate lysis products of coagulation factors, primarily fibrinogen, or their change under the influence of thromboplastic substances.

For example, in patients with diabetes mellitus, the aggregation of platelets and erythrocytes increases with a decrease in the deformation of the latter and an increase in blood viscosity. A

connection was found between heredity to atherosclerosis and hyperlipoproteinemia and an increase in the adhesive-aggregation function of erythrocytes.

The importance of changes in blood rheology and hemostasis as a risk factor for coronary artery disease, as well as the relationship with them, has also been proven.

Impaired hemostasis and fibrinolysis in hypertension

Hypertension and secondary hypertension are one of the leading risk factors for coronary artery disease. Arteriole lesions in arterial hypertension of any genesis draw attention to the role of changes in the system of hemostasis and fibrinolysis in aggravating microcirculation disorders. A number of studies have proven that arterial hypertension leads to an increase in blood clotting activity and inhibition of fibrinolysis, the intensity of which increases with the progression of the disease.

In hypertension, especially in the malignant course, there is a decrease in hematocrit, a decrease in the level of antithrombin 111 (AT 111) and the number of platelets, as well as a decrease in fibrinolytic activity of the blood. There is also evidence of an increase in the level of AT 111 in patients with hypertension.

At the same time, there are indications in the literature of less pronounced hemoagulation changes in atherosclerosis in combination with hypertension.

The presence of hypercoagulability in 0.5% of cases, accompanied by depression of the anticoagulation system in patients with subendocardial myocardial infarction in combination with systolic hypertension, was established. Some authors noted an increase in catabolism of labeled fibrinogen as hypertension stabilized. An increase in the activity of blood coagulation activity and inhibition of fibrinolysis from the 1st to the 111th stage of the disease was established. According to foreign authors, in patients with essential hypertension, as well as in an experiment in rats with hypertension, an increase in the level of prostrocyclins was recorded. However, it has not yet been established whether proscocyclin levels remain high in the long-term course of hypertension. In long-term hypertension, under the influence of catecholamines, kinins and angiotensin, blood viscosity increases, adhesive and aggregation functions are enhanced, which contributes to the progression of atherosclerosis.

Thus, the data available in the literature indicate that in patients with hypertension, disorders in the system of hemostasis and fibrinolysis have their own characteristics [16/18/19].

Hemostasis, fibrinolysis and smoking

Smoking is one of the risk factors for coronary artery disease. A five-year study in Japan found that men and women who smoke have a nearly 50% higher risk of dying from CHD than non-smokers. The incidence of new cases of CHD associated with smoking is 20%.

Nicotine, being a stimulator of the sympathetic-adrenal system, increases the level of catecholamines in the blood, the adhesion of platelets, which contributes to thrombus formation. It has been established that smoking damages the function of platelet microsomal enzymes: cyclic endoperoxidase of platelet membranes under the influence of thromboxane synthetase is transformed into thromboxane A-2, which is a powerful vasoconstrictor and provokes platelet aggregation.

A significant increase in serum thromboxane B-2 was found in smokers. In the studies of foreign authors, an increase in the adhesive properties of platelets and a shortening of their duration was observed in smokers, compared to non-smokers. Some researchers have shown that smoking even one cigarette enhances platelet aggregation, which contributes to the formation of circulating platelet aggregates in the blood of smokers. It has been proven that 20 minutes after smoking a cigarette, the reaction of beta-thromboglobulin release from alpha-granules of platelets is sharply accelerated, which confirms the activation of the platelet release reaction.

The study of the properties of erythrocytes has shown that in intensive smokers, the deformability of erythrocytes increases due to the increased content of carboxyhemoglobin in the blood, which thereby contributes to an increase in blood viscosity.

A number of researchers have established a trend towards hypercoagulation in smokers compared to non-smokers. Heavy smokers have high levels of plasma fibrinogen, lower levels of plasminogen and plasminogen activator, and higher blood viscosity compared to non-smokers.

Thus, it can be concluded that smoking contributes to the development of coronary artery disease, the progression of atherosclerosis, leads to a violation of the system of hemostasis and fibrinolysis and the occurrence of thromboembolic disorders.

Hemostasis, fibrinolysis and lipid metabolism disorders

At present, numerous data have been accumulated on the effect of lipids on the hemostosis system and rheological properties of blood. An increase in the concentration of lipids and lipoproteins in the blood and their penetration into the intima not only increases its damage, but also dramatically changes the state of blood coagulation at all phases of blood clot formation compared to individuals with normolipidemia. The potentiating effect of glycoproteinemia, especially type 11, on changes in the coagulation system of fibrinolysis in the presence of factors

such as smoking and hypertension has been established. The highest levels of fibrinogen are found in individuals with elevated blood lipids.

A positive correlation between the concentration of beta-lipoproteins, cholesterol and fibrinogen was revealed. It was reasonably concluded that platelets and fibrinogen are involved in intravascular (parietal) thrombosis at the earliest stages of atherosclerosis and coronary artery disease.

According to other authors, a low content of plasminogen activator, an increase in the activity of factor X111 and the concentration of fibrinogen were found in patients with CHD with 11 and 1U types of hyperlipoproteinemia. The observations of V.A. Lyusov and co-authors made it possible to establish that the most atherogenic types of HFR (11 and 1U) are characterized by a decrease in the time of fibrinogen circulation, which is also a direct confirmation of the important role of a component of the blood coagulation system in the genesis of interstitial and intravascular fibrin deposition as a risk factor for coronary artery disease.

There is extensive literature on the importance of hyperlipidemia in platelet dysfunction. The most studied link is the process of increasing adhesion and aggregation of platelets in hyperlipoproteinemia. An increase in platelet aggregation leads to the formation of aggregates in blood plasma that increase the concentration of specific platelet proteins and impede microcirculation. Increased platelet adhesion and shortened life expectancy in patients with hyperlipidemia are indicated.

Some authors have established a certain relationship between the type of lipid metabolism disorder and platelet activity. The reason for the increased activity of platelets in type 11 is the several times high sensitivity of platelets to ADP, adrenaline and collagen.

The identification of different forms of angina pectoris allowed the authors to identify the consumption of platelet aggregates in cases of vasospastic angina pectoris as the most pronounced changes in platelet hemostasis.

Hemostasis, fibrinolysis and overweight

Among the many risk factors that lead to the development of CHD is obesity. Excess weight predisposes to an increase in blood viscosity, which may be associated with hemoconcentration phenomena and an increase in the adhesive-aggregation capacity of platelets, as well as with inhibition of fibrinolytic blood activity.

It is known that under the influence of an atherogenic diet in the body of animals, there is a decrease in the activity of anticoagulation mechanisms leading to the development of atherosclerosis, thrombosis and thrombotic disorders.

An increase in the activity of the blood coagulation system, a decrease in the activity of anticoagulation blood and its fibrinolytic component are most pronounced in patients with angina pectoris and an increase in body weight by 20% or more compared to the ideal one.

The importance of a balanced diet in maintaining hemostatic balance is pointed out by U.A. Merserjakova and co-authors. The authors note that an increase in the quota of proteins in food contributes to the inhibition of fibrinolytic activity and an increase in the content of fibrinogen in the blood.

Hemostasis, fibrinolysis, gender and age

Approaches to the prevention of CHD and atherosclerosis should be differentiated according to sex and age. As we age, PA decreases, with a decrease in plasminogen activator and an increase in alpha1-antitrypsin and alpha-2-macroglobulin. In the first hours after birth, children's FA is elevated, and plasminogen levels are significantly reduced. Fibrinolytic activity in the blood of pregnant women is reduced, mainly due to an increase in the amount of fibrinolysis inhibitors.

Aging, as a natural process, and atherosclerosis, as pathological, alter many hemostatic functions of the body.

In the literature, there is information about the increase in blood coagulation activity with age in practically healthy people, as well as in patients with atherosclerosis and coronary artery disease. For example, according to some authors, signs of thrombophilia appear with age in practically healthy people: coagulation activity increases, plasma fibrinolysis decreases, adhesive activity increases, and platelet disaggregation and fibrinolytic activity decreases. Patients with angina pectoris experience similar changes with age. However, in patients with coronary artery disease, the severity of hypercoagulability, inhibition of fibrinolysis, and an increase in the adhesive and aggregation activity of platelets are more pronounced. According to the research, it has been proven that patients with acute MI of young age have signs of DIC blood syndrome in phases 1-2: hypercoagulable shifts in plasma with a decrease in the number of platelets and an increase in the content of fibrinmomer complexes. In elderly people with acute MI, plasma, platelet, and total plasma-platelet links of the hemostasis system, the same changes are detected as in young patients. Along with an increase in the concentration of total fibrinogen with aging of the body, the content of pathological fibrinogen B increases.

Evidence on sex differences in FA levels is mixed. A-111 levels are slightly lowered in women of childbearing age, as well as older men, compared to the rest of the population. These sex and age differences may be due to changes in estrogen-testosterone balance.

The analysis of literature data allows us to conclude that with age, the blood clotting potential of people increases, so thrombosis of the coronary vessels occurs more often in elderly patients.

Impaired hemostasis and fibrinolysis in atherosclerosis

In atherosclerosis, along with impaired microcirculation, there is a disorder of the rheological properties of the blood. Numerous studies have proven the connection between atherosclerosis and blood cholesterol levels and impaired hemostasis and fibrinolysis.

The work of many researchers shows that the development and progression of atherosclerosis depends on how and in what condition certain classes of lipoproteins are. Impaired lipid metabolism as a risk factor is associated with changes in other risk factors for the development of coronary artery disease.

At present, numerous data have been accumulated on the effect of lipids on the hemostasis system and rheological properties of blood. An increase in the concentration of lipids and lipoproteins in the blood and their penetration into the intima not only increases its damage, but also significantly changes the state of blood coagulation at all phases of blood clot formation compared to individuals with normolipidemia. The potentiating effect of lipoproteinemia, especially type 11, on changes in the blood coagulation system and fibrinolysis in the presence of such factors as smoking and hypertension has been established. The highest levels of fibrinogen are found in individuals with elevated blood lipids. That is, it was reasonably concluded that platelets and fibrinogen are involved in intravascular ()parietal thrombosis at the earliest stages of atherosclerosis and coronary artery disease.

There are theories according to which the metabolism of fibrinogen is carried out through the permanent conversion of part of it into fibrin, which lines the endothelium with a thin layer, and penetrating into the intercellular clefts, "cements" the vascular wall, playing an essential role in regulating its permeability. With an increase in fibrinolytic activity, the film thins and this is fraught with bleeding, with a decrease, on the contrary, it thickens, being a substrate of sclerosis.

Impaired fibrinolysis in rheumatism

In the analysis of works devoted to the study of the activity of the fibrinolysis system in patients with rheumatism, some authors find inhibition of fibrinolysis and associate this with an increase in plasmin inhibition and the mechanism of plasminogen activation. There is an opinion that the phase of shifts in fibrinolytic activity is due to the degree of allergy of the body, which underlies the multidirectional changes in fibrinolytic activity. In addition, the fibrinolysis system in rheumatism is influenced by other factors, in particular, circulatory insufficiency, damage to the kidneys, liver, spleen, nervous system, microthrombosis in small vessels. The same applies to fibrinolytic activity in circulatory insufficiency, which complicates the course of rheumatic

heart defects. Increased fibrinolysis activity is often observed with clinically pronounced decompensation, especially in the inactive stage of rheumatism. Finally, the study of regional fibrinolysis indicates a decrease in its pulmonary artery blood in hypertension and congestion in the pulmonary circulation.

CHANGES IN HEMOSTASIS AND FIBRINOLYSIS IN CORONARY HEART DISEASE

Impaired blood flow and blood circulation in general is a prerequisite for the development of diseases of the cardiovascular system. The conditions of blood circulation in small and medium-sized vessels, and to a lesser extent the width of the vessels, depend not only on the propulsive activity of the heart, but also on the biological properties of the blood itself, which determine its fluidity. The aggregation mechanism is mainly reduced to the elimination of the surface negative charge and the formation of a fibrin bridge between cells. This leads to the cells getting closer to each other. The entire aggregation of erythrocytes impedes blood flow through small vessels, sometimes to the point of blockage, leading to ischemia and necrosis of organs. In case of vascular stenosis, there is a vortex of the "dead" zone, the zone of stagnation, which is united by a single term turbulent current. This type of blood flow is a prerequisite for the sedimentation of the forms of the elements and the development of thrombosis.

Numerous clinical studies have established the important role of hypercoagulation, depression, fibrinolysis, platelet disorders and lipmid metabolism in the pathogenesis of atherosclerosis and coronary artery disease, coronary atherosclerosis. It is known that already in the early stages of coronary artery disease, significant changes in the blood coagulation system are detected.

In acute myocardial infarction (MI), coronary thrombosis occurs up to 80%. Thrombosis in intact coronary arteries may be based on local spasm due to an increase in platelet properties and the release of vasoactive substances. In some patients with MI, an increase in platelet aggregation capacity was found associated with hypercatecholanemia, an increase in the content of lactic acid and free fatty acids, and the release of serotonin and other substances from blood platelets.

At present, in addition to platelets, which are cell regulators, humoral physiological anticoagulants – inhibitors of proteolytic blood enzymes – are of great importance in the system of regulation of the aggregant state of blood.

It has been established that the pathogenesis of most prethrombotic conditions and thromboembolic diseases is directly related to the deficiency or inhibition of these protein substances.

In acute MI, there is a close inverse correlation between the functional properties of platelets and the activity of blood callecrein. In complicated MI, in contrast to uncomplicated MI, in the acute period of the disease, there is a significant decrease in the antiheparin activity of platelets and a sharp increase in the activity of callecrein in the blood. In the subacute period, the secretory capacity of platelets remains reduced compared to normal, but higher than in the acute period. In the acute period of MI, the number of platelets, their adhesive, aggregation activity, thromboplastic activity of the blood increases due to the intake of thromboplastin from the vascular wall and the focus of necrosis, and the fibrinogenic tolerance of plasma to heparin increases. An important role in the pathogenesis of MI is played by disorders of the rheological properties of the blood, which lead to a progressive deterioration of the MC and the development of thrombosis in conditions of stenotic vasoconstriction. It is known that these disorders are largely the result of changes in the protein composition of plasma and the biophysical characteristics of formed elements, primarily erythrocytes and platelets.

Studies in recent years have suggested the active participation of the vascular wall in the regulation of adhesion and aggregation of formed elements. This participation can be realized through a change in the intravascular blood supply. And the release of a number of biologically active substances with anticoagulant, antiproplatelet and fibrinolytic activity.

A significant increase in platelet coagulant activity was found in patients with retrosternal pain and angiographically confirmed CHD compared to healthy people. In the pathogenesis of unstable angina, the leading role is played by the disorder of thrombogenesis, the morphological substrate of which is recognized as an intracoronary non-occlusive thrombus, as well as hemostasiological changes in the blood flow system. It is believed that the occurrence of thrombotic coronary artery occlusion is determined by the local state of hemostasis, which cannot be assessed by peripheral blood parameters. Factors such as hypertension, hyperlipidemia, hormonal dysfunctions, and substances secreted from hyperreactive platelets can cause damage to the endothelium, which is accompanied by platelets sticking to the vascular wall. At the same time, platelets attached to the endothelial layer aggregate and release fibrinogen, beta-thromboglobulin, adenosine diphosphate, serotonin, histamine and factor 4 from alpha granules, which in turn cause damage to the vascular wall.

It has also been established that the determining role in changing the aggregate state of blood belongs to metabolic disorders of endogenous protonsoids and cyclic nucleotides, the most important natural humoral regulators of physiological functions.

It is also suggested that in response to psycho-emotional stress, there is a significant increase in the functional activity of the hemostasis system, which consists in an increase in the

functional activity of platelets and procoagulant activity of the blood, a decrease in the anticoagulant and fibrinolytic activity of the blood and the antithrombogenic activity of the vascular wall, which is largely associated with the reactions of the sympathetic-adrenal system. One of the diagnostic signs of prethrombotic conditions is a decrease in blood fibrinolytic activity due to a decrease in the level of plasminogen activators, a decrease in plasmin concentration, an increase in the content of antiplasmins, and an increase in the level of fibrinolysis inhibitors. The protective properties of non-enzymatic fibrinolysis are significantly reduced in depression of the anticoagulation system, especially in hypercoagulable conditions observed in patients with coronary artery disease.

E.P. Panchenko and co-authors, studying the content of fibronectin in the blood of the coronary sinus in patients with CHD during angina attacks caused by atrial stimulation, found a decrease in the concentration of fibronectin. The authors attribute this decrease to the antithrombic function of fibronectin. When studying the peculiarities of the relationship between the hemostasis system and the level of fibronectin in patients with coronary artery disease, a significant increase in the concentrations of fibrinogen and PDF and a decrease in the level of fibronectin in patients with CHD with a slight change in other indicators of the thrombogenesis system were established. It is concluded that an increase in the levels of fibrinogen and PDF indicates a state of tension both in the thrombogenesis system and in the fibrinolysis system, which generally characterizes an increase in the activity of the hemostasis system, which is combined with a decrease in the activity of the phagocytic link of immunity and the function of lymphoid tissue. An increase in the concentration of fibrinogen and PDF in combination with a decrease in the level of fibronectin is regarded as the presence of dysproteinemia.

Analysis of the literature data shows that there are practically no population studies to study the role of disorders in the systems of hemostasis, fibrinolysis and microcirculation, at the same time, without taking them into account, it is not possible to obtain a more objective comprehensive assessment of the epidemiological situation with regard to CHD in the population.

In this regard, we conducted a study on this important problem in modern cardiology on the topic: "Population-genetic aspects of changes in the systems of hemostasis, fibrinolysis and microcirculation in coronary heart disease".

RESEARCH RESULTS

INVESTIGATIONS

In order to identify the occurrence and development of new cases of **Coronary Heart Disease (CHD)** and mortality due to some of the main risk factors, disorders in the system of hemostasis and microcirculation, we conducted an epidemiological and prospective study of the prevalence of CHD and its risk factors – hypertension, **Body Mass Index (BMI)**, hyperlipidemia, smoking, alcohol consumption, family predisposition, etc. in the indigenous and non-indigenous population of men and women aged 40-54 years. The respondents lived in the same social, domestic, climatic and geographical conditions of the city of Andijan. In order to present a real picture of the prevalence of coronary artery disease, the studies present standard methods for detecting CHD and its risk factors. When developing the methodology, we tried to ensure that it was adequate and met the following WHO requirements:

1. The methodology must be valid, i.e. provide a measurement of what needs to be measured.
2. It must be sufficiently reproducible and accurate.
3. The technique should be convenient and practicable in the conditions for which it was intended.

1. Selection of the population for the survey

In accordance with the goals and objectives of the study, the male and female population aged 40-54 years, representing the indigenous and non-indigenous population of Andijan of the Republic of Uzbekistan, was chosen as an object.

Characterization and sampling.

To study the prevalence of CHD and its risk factors associated with disorders in the systems of hemostasis, fibrinolysis and microcirculation, an epidemiological and prospective study of the unorganized population of the city was carried out.

The total number of indigenous and non-indigenous population of Andijan was 15,526 people. From this array, a proportional 10% sample was formed by the method of random numbers, which amounted to 1,553 people. There were 712 males and 462 females The survey coverage was 75.5%.

The following points were taken into account when organizing the sample:

1. Migration of the population is minimal
2. The population of the selected district for the survey shall be representative of the entire inhabited locality.
3. The survey area is well connected by transport to the survey site

4. The number of persons to be examined is sufficient to ensure the statistical reliability of the results

5. The survey was carried out in an area not spared by other population surveys.

Survey Methods and Program

To identify CHD and its risk factors in the population and among family members of probands, a survey was carried out according to the following program:

A.Epidemiological study

1. Standard Cardiology Questionnaire (Rose Questionnaire)
2. Anthropometry (height and weight)
3. Blood pressure measurement
4. Bad habits (smoking, drinking alcohol)
5. ECG recording at rest, followed by interpretation by Minnesota code.

B.Biochemical research

1. Study of lipid parameters:

A) Determination of total cholesterol (TC) in blood serum

B) serum triglyceride (TG) levels

C) high-density lipoprotein (HDL-C)

D) Low-density lipoprotein (LDL-C)

2. Studies of hemostasis and fibrinolysis system indicators:

A) Quantification of FDPs (biochemical and immunological method)

B) antithrombin level – **III**

C) the number of soluble fibrin monomer complexes

D) Quantification of fibronectin

E) Time of thrombin formation

E) free heparin

G) Prothrombin Index

H) Ethanol Test

I) fibrinogen

C) Examination of the Blood flow index (BFI) **of the conjunctiva of the eye using the biomicroscopic method** with a slit lamp SCHL-2B, SCHL-56 with a magnification of 30 to 60 times.

Intervention program aimed at correcting the identified risk factors

The means of **vasoaction** on the disorders in the hemocoagulation and microcirculation systems detected during a single-stage epidemiological study was mainly aspirin, less often trental.

Aspirin was given to patients with hemostasis and microcirculation disorders at 0.5 every other day or 0.25 every day for 2 months, some of them are recommended to take Trental 1 tab. 3 times a day.

To carry out this work, 200 people (with hypercoagulation, disturbance in the microcirculatory system, CHD) were randomly selected for intervention: 100 of them were in the intervention group (HB) and 100 people in the control group. In 2 months after the start of the intervention, a repeat examination was carried out according to the full program (Rose questionnaire, study of hemostasis, fibrinolysis, MC, lipid metabolism, clarification of changes in the general condition of the examined, etc.)

Family Study

An additional study was conducted to identify the role of familial predisposition in the development of CHD, as well as to identify CHD and risk factors in the population and among family members of probands.

From among the men and women aged 40-54 years from the general population, 10% of people with impaired hemocoagulation and MC, CHD, or without it were randomly selected probands. The examination of family members of probands (80 men and women) was carried out according to the above-mentioned program. Spouses (husbands and wives) and siblings (brothers and sisters) of probands (150) aged 40-54 years were invited to the examination. Heredity was considered to be aggravated in persons whose parents under the age of 55 suffered from cardiovascular diseases (CHD, hypertension).

Prospective research

In order to detect the occurrence of new cases of CHD and mortality due to some of the main risk factors, disorders in the hemostasis and microcirculation systems, prospective observation was carried out in persons (592 men, 346 women) examined during a one-stage study (after 5 years). From among those examined for the prospective study, persons in whom CHD was not detected during the initial study and persons with possible CHD were selected. Persons with CHD were excluded from the total number of examined. The prospective study provided for a full-time examination of the first visit, with the aim of detecting new cases of CHD over a period of 5 years.

Methodologies

Lipids (cholesterol, TG, alpha-cholesterol), hemocoagulation indicators were studied at the Republican Clinical Laboratory Center at the Central Republican Clinical Hospital of the Ministry of Health of the RSFSR. Determination of fibronectin and FDPs was also carried out

at the Laboratory of Immunochemistry of the All-Russian Scientific Center of the Academy of Medical Sciences of the Russian Federation.

Blood was taken on an empty stomach, at least 12-13 hours after meals, from the ulnar vein, in compliance with all the requirements for blood collection and storage. A solution of sodium citrate was used as a stabilizer. The ratio of blood to preservative was 9:1 with normal hematocrit. The appearance of the serum (clear, cloudy, milky, creamy) was assessed, as well as the presence or absence of a layer of floating chylomicrons when the serum is standing. A 0.1% solution of sodium azide was used to preserve the blood. Blood (plasma, serum) was stored in the Schneck refrigerator at 20 degrees, sub-zero mode.

Biochemical research methods. The content of total **CH**, TG and HDL-C was determined in blood serum using an autoanalyzer FP-901.

Blood sampling for the study was carried out after a 12-hour fast. Extraction of CS and TG from serum was carried out with isopropyl alcohol at the rate of 1**:**20**.**

The concentration of cholesterol was determined by the **Abel-Kendall** method. HDL-C was determined in a supernatant after precipitation of LDL-C and VLDL-C with heparin in the presence of manganese.

The TG concentration was determined by the Carlson method in the Kessler and Lederer modifications.

Examination of the system of hemostasis, fibrinolysis.

Determination of antithrombin - III.

(Barkagan method modified by Titova M.I.)

To determine the AT-SH, the ready-made heparin solution was diluted so that 1 ml of it contained 1 unit (500 ml of Ng0 + o, 1 ml of heparin - 500 units). Before the work, heparin solution was diluted in the ratio: 1 ml of solution (1 u/1 ml): 10 ml of saline solution, at which there was 0.1 unit. In 1 ml. Thrombin was used for 20-22 seconds. Activity. Thrombin time was determined. Plasma + heparin solution was added to the second tube. Thrombin prolongation time was observed.

Definition of FDPs

(Nanning and Guest's method modified by G.V. Andreenko) and Podolskaya D.V.)

To perform this work, 4.6 ml of medinal buffer and 0.2 ml of thrombin are added to 0.4 ml of plasma. The mixture is incubated for 1.5 hours at 37 e. The resulting clot is squeezed on a glass stick and discarded, or further used to quantify fibrinogen according to the Bidwell method. 2.5

ml of 0.85% sodium chloride solution and 2.5 ml of saturated sodium chloride solution are added to the liquid remaining after the curd has been squeezed. Then everything is done as in the original method. The differences are as follows:

After heating, the FDPs precipitate is dissolved in 1 ml of 0.1 n. **NaOH**, boiled for 30 minutes at 100°, brought to 1 ml with water and determined the protein according to the Lowry method.

Calculation of FDPs $\text{FDPs (mg/dL)} = \frac{Uh}{4}$

Where Uh is the amount of protein (μg/ml) determined by the normal FDPs curve from O to 10 mg/dL.

Niviarovsky and Gurevich protamine sulfate test for the determination of soluble fibrin

The method is based on the cleavage of high-molecular complexes of fibrin monomer with FDPs by the main protein protamine sulfate. Gel formation or precipitation in the form of filaments or bundles indicates the presence of either fibrin monomer or its complexes with FDPs. The test is sensitive at fibrin monomer concentrations of 2 to 5% and 5 to 10 mg% of early FDPs s.

The following dilutions of freshly prepared 1% PS solution are prepared. in 0.85% NaCL, pH 6.0 - 1:5, 1:10, 1:20, 1:40, 1:80. 0.2 ml of platelet-poor citrate plasma is poured into Sali's test tube. The tubes are left for 30 minutes at room temperature, then tested in direct light and on an unreflected black background. The appearance of sediment is assessed as follows: gel formation (G), fibrin strands (FT), fine sediment (+), coarse sediment (+), pure solution (-).

The test is considered positive if the formation of strands and gel occurs with any dilution. The test is negative in normal plasma and primary fibrinolysis, positive in diffuse intravascular coagulation and in fibrin dissolution by thrombolytic drugs.

Determination of thrombin time. (Sirmai Method 1)

The method is based on determining the time of plasma clot formation when an excess of thrombin is added to it. It allows the determination of antithrombin, including heparin.0.0 ml of test **plazma** and 0.05 ml of saline solution are injected into an agglutination tube. The test tube is placed in a water bath at 37°. After 10 seconds, (at least 30 minutes) 0.1 ml of thrombin solution is added. The time of plasma clotting is noted. Normal thrombin time is equal to the activity of the donor's plasma thrombin, which is called thrombin.

A lot of heparin (antithrombin) - the time of clot formation is prolonged. This is seen with a tendency to hemorrhages.

Free blood heparin test. (Sirmai Method 1)

The method is based on the ability of toluidine blue to bind free heparin in the blood. The introduction of a solution of toluidine blue instead of saline leads to a shortening of thrombin time in accordance with the quantitative content of free heparin in the blood.

In the **agglutination** tube, measure **0.05 ml** of saline + **0.1 ml** of test plasma. The test tube is placed in a water bath at 37 C. After 30 seconds. 0.1 ml of thrombin is added and the plasma clotting time is noted.

The difference in blood clotting time between the 1st and 2nd tubes indicates the amount of free heparin. Normally, it is 16-20 seconds (7-10 seconds). The relationship is direct, the greater the difference, the more heparin.

The determination of the concentration of fibrinogen in plasma was carried out by the dry-air method of R. A. Rutberg in the modification of **W. K. Peters**, which is well known, so its description is not given.

Ethanol Test

The method is based on the formation of a gel in plasma after the addition of a 50% ethanol solution.

0.15 ml of 50% ethanol solution and **0.5 ml** of plasma are injected into the tube, the tube is shaken and placed in a rack at room temperature.

If a gel forms in the test tube after 1-3 minutes, the sample is considered positive (1). Cloudiness or slight graininess – negative (0).

Determination of prothrombin activity was carried out by the Quick method modified by B.A. Kudryashov 1, which is well known, so its description is not given.

Determination of fibrinogen and FDPs *by immunochemical method.*

A test system was used to determine fibrinogen and fibrin-fibrinogen degradation products. The basis of the solid-phase enzyme-linked immunosorbent assay is the high-contact binding of antibodies to fibrinogen with the surface of polystyrene, as a result of which it acquires the properties of an antibody sorbent capable of extracting fibrinogen or FDPs from biological fluids. Next, the enzymatic activity is measured by the change in the color of the substrate mixture. Color change is recorded either visually or calorimetrically on a multichannel spectrophotometer at a wavelength of 492 nm.

The test system is specific for fibrinogen and fibrin-fibrinogen degradation products and allows detecting them in an amount of 40 ng/ml. The norm for FDPs is 15-26 μg/ml, fibrinogen is 2-6 mg/ml.

Method of quantitative enzyme-linked immunosorbent determination of fibronectin

Rabbit antibodies to human fibronectin were used for mobilization on lystyrene plates. Antibodies were added to the plate wells of **200 µl** in a carbonate buffer of 0.01 m. pH 9.6 (protein content 10 mg/ml). The plates were incubated for 15-18 hours at 37 °C, then repeatedly washed with tap water with 0.06 twin 20 and 200 µl of blood plasma samples diluted 1:1000 with phosphate-salt buffer pH 7.2. The specimens were incubated in wells for 30 min at 37° C. The wells were washed again as indicated above, and 200 ml of diluted antifibronectin antibody conjugate with peroxidase was added to each of them. The conjugate was incubated for 30 min at 37° C. and, after washing the plates, 200 µl of a substrate mixture consisting of a 0.0015% water solution with a 0.01% orthophenylenedeamine solution in a pH 4.7 citrate buffer was added to each well.0,06 M

After incubation for 10 minutes at room temperature, the reaction was stopped by adding 50% sulfuric acid to 60 µl wells. The color intensity of the substrate mixture was measured photometrically at a wavelength of 492 nm.

A standard calibration curve was obtained using fibronectin, the isolation of which is described above. Fibronectin for the calibration curve was diluted in phosphate-buffered salt with 0.06% twin 20 pH 7.2-7.4. As a result of the analysis of a series of calibration curves obtained, including the following amount of fibronectin: 800, 400, 200, 100, 60, 26, 12.6, 6.26 ng/ml. The content of fibronectin in the studied blood plasma samples was determined according to a standard calibration curve. Standard The dilution of fibronectin for the construction of the calibration curve was prepared for each plate. Normal fibronectin values are 330+76 µg/ml.

Blood pressure measurement. During the examination, the methods of blood pressure measurement proposed by the World Health Organization were used. BP was measured after a 5-minute rest four times on the right arm in a sitting position at regular intervals. The analysis used the average of four BP measurements. Systolic blood pressure (SBP) of 160 and/or diastolic blood pressure (DBP) of 96 mmHg were taken as hypertension. Art.; The group of patients with hypertension also included people who took antihypertensive drugs during the examination period or stopped taking them in less than 2 weeks.

Methods for diagnosing coronary artery disease. To diagnose coronary artery disease, a survey was used on the WHO questionnaire for the detection of angina pectoris. All staff who conducted the survey were standardized and certified. The "strict criteria" for angina pectoris were used in the analysis, i.e., angina pectoris. Only retrosternal pain, or pain in the left side of the chest with radiation to the left arm, which occurs when walking and disappears within 10 minutes after stopping or taking nitroglycerin.

Anthropometric research methods. Body weight was measured using a medical lever scale in a standing **POSITION**. The accuracy of body weight measurement is up to O, 1 kg. Height was measured with a height gauge with an accuracy of up to . Quetelet index was used as the overweight index (BMI):0,6 см

$$\text{- - - - - - - - - = (I K) I N D E X K E T L E} \quad \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$$

BMI was set at I K values > 29 kg/m2.

Collection of information on smoking. In relation to smoking, the subjects were divided into the following groups: 1. smokers; 2. Never smoked; 3. quit smoking more than 2 years ago; 4. Quit smoking less than 2 years ago. In addition, the number of cigarettes smoked was taken into account. A smoker was defined as a person who smoked at least 1 cigarette daily or who had stopped smoking less than 12 months earlier.

Consumption of alcoholic beverages. In connection with the possible influence of alcohol on the occurrence of CHD and its risk factors, all examined persons were asked questions clarifying the type, amount and frequency of alcohol intake.

Examination OF CONJUNCTIVAL VASCULAR microcirculation. Biomicroscopy is one of the main methods for studying MC from thevessels of the conjunctiva of the eye.

The method of studying MC processes is often used in the clinic and experiment. The use of this method in population-based studies according to the literature is rare. There are two methods: contact and non-contact biomicroscopy. We used the non-contact method, using slit lamps SCHL-56 and 2B. Biomicroscopy is not very difficult, since the main parts of the conjunctiva are easily accessible to examination with a slit lamp.

The study took into account conditions that may affect the state of the MC (eye disease, medication, etc.). The temporal part of the bulboconjunctiva, the limbal region, and the conjunctiva of the inferior transitional fold were observed as the most accessible areas.

During the biomicroscopy of the conjunctival vessels of the eye, attention was paid to perivascular, vascular, and intravascular changes, and the ratio of the diameter of the arteriole and venule was taken into account.

Assessment of the state of the microvasculature bed

1. Perivascular changes:

(a) hemosiderosis;

b) Hemorrhage;

c) deposition of: lipids, cholesterol;

d) perivascular edema;

e) No;

2. **Arteriolye:**

(a) total number of arterioles: normal, decreased, enlarged;

b) arteriole caliber: normal, narrowed, irregular;

c) Nature of the skylight: flat, uneven, desolate;

d) aneurysms: spindle-shaped, sac-shaped, single, multiple, none;

e) tortuosity: normal, enlarged, straightened;

3. Venules:

(a) Venule caliber: normal, narrowed, dilated;

b) skylight: flat, uneven, desolate;

c) aneurysms: spindle-shaped, sac-shaped, single, multiple, none

d) tortuosity: crmal, enlarged, multiple, none

4.Capillaries:

A) Arcade, Correct Distribution Pattern, Incorrect Distribution Pattern, Aneurysms, Tortuosity

C) venous part: normal, narrowed, dilated, aneurysms, tortuosity

5.Blood Flow Characteristics

A) Arterioles: deceleration, retrograde, block, acceleration, normal, intermittent current, sludge

B) Venules: Slow, Retrograde, Block, Acceleration, Normal, Intermittent Current, Sludge;

C) Capillaries: Deceleration, Retrograde Current, Acceleration, Normal, Intermittent Current, Sludge.

6. Arteriole, venule ratio:A:B

Based on the results of the analysis, risk functions were constructed to assess the risk of new cases of CHD depending on the value of the generalized SF, which is a linear combination of selected informative SF.

The adequacy of the selected model to the initial data was checked by comparing the theoretical and empirical number of cases in the quartiles of the generalized risk factor according to the X-squared criterion. With statistical values of X-squared more than 0.06, the adequacy of the model was ascertained.

The analysis of the genetic material was reduced to the assessment of the correlation coefficient between the main SF and the disorder in the hemostasis system, MC (after adjusting for age). The distribution of parameters in relatives of probands with disorders in the systems of hemostasis, fibrinolysis and MC was studied.

PREVALENCE OF CHD AND MAJOR RISK FACTORS IN THE POPULATION

Prevalence of major risk factors

The population under study is characterized by a very wide prevalence of arterial hypertension, which was observed in 44.4% of men and 57.9% of women (Table 1). Differences in the prevalence of hypertension in indigenous and non-indigenous populations are multidirectional in men and women. In indigenous men, hypertension is 4.8% more common than in non-indigenous men ($p< 0.001$), and in women, on the contrary, it occurs 5.6 times more often than in non-indigenous men ($p< 0.01$).

Age-related features of hypertension prevalence are insignificant. In men, the difference in prevalence is only 1.1%, between the younger and older groups, with hypertension being less common in the older group than in the younger group. In women in the older age group, hypertension is 11.8% more common ($p< 0.01$).

DLP in the studied population was recorded in 40.6% of men and 42% of women (Table 2). In men, there is an increase in the number of cases of DLP with age ranging from 32.7% in the younger group to 46% in the older group ($p< 0.01$). However, these differences are more pronounced among indigenous populations than among non-indigenous populations.

In women, DLP was most common at the age of 45-49 years, and the prevalence of DLP in the older group even decreased. In all age groups, DLP was more common in the non-indigenous population, which can be explained to some extent by differences in nutrition.

Table 1. Prevalence of arterial hypertension in age-sex and national groups

Age	**Indigenous**		**Non-indigenous**		**Altogether**	
	M	**m**	**M**	**m**	**M**	**m**
Men						
40-44	42,9	0,04	33,7	0,08	45,1	0,04
45-49	49,0	0,04	35,7	0,06	44,4	0,03
50-54	46,4	0,04	40,3	0,04	44,0	0,03
40-54	46,0	0,02	41,2	0,03	44,4	0,02
Women						
40-44	45,8	0,05	72,0	0,10	50,4	0,04
45-49	59,1	0,05	62,8	0,05	60,7	0,04
50-54	63,3	0,05	60,4	0,07	62,2	0,04
40-54	57,4	0,02	63,5	0,04	57,9	0,02

From the data presented, it follows that CH was most elevated in indigenous men aged 45-49 years (20.9), and in non-indigenous men aged 50-54 years (26.7). Among women, the highest (35.0) HCH was in the non-indigenous population aged 40-49 years, among the indigenous population 50-54 years. TG was highest in indigenous men aged 50-54 years (40.5) and in non-

indigenous men aged 45-49 years. Among women, TG was higher at the age of 45-49 years (non-indigenous and indigenous). The largest decrease in alpha-C was among non-indigenous men aged 40-44 years (28.6) and non-indigenous women (66.7) in this age group.

Table 2. Prevalence of DLP by Age, Sex and National Groups

Age	Indigenous		Non-indigenous		Altogether	
	M	m	M	m	M	m
Men						
40-44	30,2	0,04	41,2	0,08	32,7	0,04
45-49	39,0	0,04	40,0	0,06	39,3	0,04
50-54	47,4	0,04	43,8	0,05	46,0	0,03
40-54	39,7	0,01	42,2	0,04	40,6	0,02
Women						
40-44	35,8	0,05	52,1	0,10	38,6	0,04
45-49	38,9	0,05	51,3	0,06	44,6	0,04
50-54	34,7	0,06	53,3	0,07	41,9	0,05
40-54	36,5	0,03	52,1	0,04	42,0	0,02

BMI prevalence data show that 23.9% of men and 27.3% of women have BMI. Men in all age groups had a lower BMI than women ($p < 0.001$). However, it should be noted that 44% of young women of non-indigenous nationality have BMI. This indicates that there is insufficient propaganda about the harm of obesity among the population.

40.6% of men and only 1.1% of women were smokers. With age, the proportion of men who smoke decreases from 49.7% to 36.7% (Table 3). It is also characteristic that the decrease in the number of smokers with age is observed only among the indigenous population, among whom smoking is 1.6 times less common ($p < 0.001$). In the non-indigenous population, the proportion of smokers aged 40-44 and 50-54 is the same.

There were no registered smokers among indigenous women. Among the indigenous population, a significant (12%) proportion of smokers is observed in the youngest age group, which is generally characteristic of the population of many regions.

Table 3. Prevalence of smoking by age, sex and nationality

Age	**Nationality**					
	Indigenous		**Non-indigenous**		**Altogether**	
	M	**m**	**M**	**m**	**M**	**m**
Men						
40-44	48,7	0,04	53,7	0,08	49,7	0,04
45-49	29,4	0,04	54,8	0,06	38,0	0,03
50-54	25,4	0,04	53,8	0,05	36,7	0,03

40-54	34,7	0,02	54,1	0,03	40,6	0,02
Women						
40-44	0	0	12,0	0,06	2,1	0,01
45-49	0	0	2,33	0,02	1,1	0,01
50-54	0	0	0	0	0	0
40-54	0	0	3,1	0,01	1,1	0,01

A characteristic feature of the studied population is significant differences in alcohol consumption (Table 4). From the above data, it can be seen that 53.6% of men and 13.2% of women were drinkers. With age, the number of people who consume alcohol decreases significantly in men and slightly in women. It is also characteristic that in all age groups, indigenous men consume less alcohol than non-indigenous men ($p< 0.001$). At the same time, indigenous people reduce alcohol consumption by 1.8 times, and non-indigenous people by only 1.1%. Indigenous women drink little alcohol (13 per cent) and only at a younger age, while 35.8 per cent of non-indigenous women consider themselves to be drinkers.

Table 4. Alcohol Consumption by Age, Sex and National Groups

Age	**Nationality**					
	Indigenous		**Non-indigenous**		**Altogether**	
	M	**m**	**M**	**m**	**M**	**m**
Men						
40-44	57,1	0,04	78,1	0,06	61,5	0,04
45-49	51,1	0,04	65,8	0,06	56,0	0,03
50-54	31,5	0,04	69,8	0,04	46,7	0,03
40-54	45,6	0,02	70,0	0,03	53,6	0,02
Women						
40-44	2,5	0,01	48,0	0,10	10,5	0,03
45-49	1,0	0,01	34,9	0,05	16,2	0,03
50-54	0	0	31,2	0,07	11,8	0,03
40-54	1,3	0,01	35,8	0,04	13,2	0,02

Thus, it follows from the data presented that CHD is a common disease affecting both indigenous and non-indigenous populations in the region. In men, certain CHD is much more common than in women. The non-indigenous population is 1.8% more likely to suffer from coronary artery disease. The most vulnerable age for men is 50-54. The incidence of CHD at a younger age (40-49 years) is noteworthy.

Our data suggest that CHD is more common among intellectual workers.

According to our data, lipid metabolism disorders in the form of an increase in cholesterol and hypoalpha-cholisteremia are highly informative risk factors for coronary artery disease.

The generally accepted risk factor for CHD in the form of smoking was identified in 40.6% of men, among young women of the non-indigenous population, smoking is 12%. It is possible that this risk factor, along with other factors, is the reason for the "rejuvenation" of CHD among women. A similar picture was obtained in the assessment of alcohol abuse, where 35% of women of nationality were drinkers.

Prevalence of CHD

When studying the prevalence of CHD in the population according to extended criteria, we obtained data close to the indicators previously presented by researchers in this region. We are inclined to explain some of the increases in the incidence of CHD in our studies by the negative influence of increasing risk factors during the study period.

Significant differences have been recorded between the prevalence of CHD in indigenous and non-indigenous populations in both men and women, and in non-indigenous people, CHD is 2 times more common ($p< 0.001$). These differences are particularly large between the prevalence of CHD in men aged 50-54 years, where the differences are 16%.

In men, there is an increase in the number of cases of CHD with age in both national groups, while in indigenous women, the number of cases of CHD in the older age group is 1.4 times lower than in the age group 45-49 years

From Table. Figure 5 shows that the prevalence of CHD is 8.2% higher among women than among men ($p< 0.001$), with 8.0% of the difference among the indigenous population and 6.4% among the non-indigenous population ($p< 0.0001$).

Certain CHD was 8.1% more common in men than in women ($p< 0.001$), with 5.1% in the indigenous population and 13.6% in the non-indigenous population, i.e. 1.8 times higher ($p< 0.001$). In men, the incidence of CHD increases with age, with the highest prevalence among the non-indigenous population aged 50-54 years, where the number of cases reached 23.5%.

Table 5. Prevalence of CHD by age, sex and nationality groups

Age	**Indigenous**		**Non-indigenous**		**Altogether**	
	M	**m**	**M**	**m**	**M**	**m**
By Advanced Criteria for Men						
40-44	10,4	0,02	22,0	0,06	12,8	0,02
45-49	14,0	0,03	24,7	0,05	17,6	0,03
50-54	13,2	0,02	26,9	0,04	18,7	0,02
40-54	12,6	0,02	25,3	0,03	16,7	0,01
Women						
40-44	21,2	0,04	24,0	0,08	21,7	0,03
45-49	22,9	0,04	36,1	0,05	28,8	0,03

50-54 40-54	16,5 20,5	0,04 0,02	33,3 33,3	0,07 0,04	22,8 25,0	0,04 0,02
Defined CHD in men						
40-44 45-49 50-54 40-54	8,4 11,2 11,6 10,5	0,02 0,03 0,02 0,01	7,3 12,3 23,5 17,2	0,04 0,04 0,04 0,02	8,2 11,6 16,3 12,7	0,02 0,02 0,02 0,01
Women						
40-44 45-49 50-54 40-54	14,4 18,1 13,9 15,6	0,03 0,04 0,04 0,02	24,0 33,7 29,2 30,8	0,09 0,05 0,07 0,04	16,1 25,1 19,9 0.04 20,8 0,02	0,03 0,03

In women, there is an increase in the number of CHD cases between the ages of 45 and 49, but there is a slight decrease in the number of CHD cases in the older group.

The obtained data differ somewhat from the generally accepted ones in the form of a high incidence of CHD in women (according to extended criteria), which, apparently, is due to the low information for women of the Rose criterion. In subsequent studies on CHD, only a specific CHD was taken into account.

There is a significant difference in the prevalence of CHD in different educational groups. In our studies, CHD was most rarely registered in people with less than secondary education, where CHD occurred in 12% of men and 18.5% in women. Among people with higher education, the number of cases of CHD in men was 2.4 times higher than in the group with less than secondary education ($p< 0.005$). In women, however, these differences are smaller, and here CHD was most often recorded among those with higher education. It is also noteworthy that in the groups of incomplete and secondary education, CHD is more common in women ($p< 0.001$), and among people with higher education, the prevalence of CHD in men and women was the same.

In men, CHD is much more common among employees than among workers ($p< 0.001$), but the maximum number of cases of CHD was registered in non-workers, which is quite understandable, since this group includes, mainly, pensioners, who are also unemployed due to disability. They were older people.

They had a more pronounced stage of CHD, since disability was mainly determined by the incidence of CHD. In women, on the contrary, CHD was more common among blue-collar workers than among employees ($p< 0.01$). The latter can be explained, apparently, by the excessively high physical and psychological burden that falls on women as a result of the combination of domestic and work loads. It should also be noted that there are no sex differences

in the prevalence of CHD among employees, although CHD is much more common among female workers than among men ($p< 0.001$).

Dyslipoproteinemia plays a significant role in the prevalence of coronary artery disease. Among individuals with DLP, CHD was 1.9 times more common in men and 2 times more common in women ($p< 0.001$) compared to no DLP. It should also be noted that in women without DLP, CHD occurred 1.4 times ($p< 0.01$), and with DLP 1.5 times ($p< 0.05$) more often than in men.

As for the differences in the prevalence of CHD between those with normocholesterolemia and those with hypercholesterolemia (Figure 3.5), as expected, among those with HCH, CHD in men was 2.7 times more common than in those with normal cholesterol levels ($p< 0.01$). In women, these differences are slightly lower, but CHD was registered 1.6 times more often among individuals with hyper-**CH** ($p< 0.05$).

There are very high differences in the prevalence of CHD between individuals with hypoalpha cholesterolemia and those with normal alpha cholesterol levels. In men with hypoalpha-C, CHD was 2.8 times more common than in normal alpha-cholesterol levels ($p< 0.001$), and in women 2.9 times ($p< 0.00$).

CHD was significantly more common in individuals with hypertension. In women, these differences were 1.5 times, and in men 1.8 times ($p< 0.01$).

And, finally, considering the relationship between CHD and overweight, it was found that with an increase in the frequency of CHD, body weight tended to increase, however, we did not get a strategically significant difference in this indicator.

ASSOCIATION OF DISORDERS OF THE HEMOSTASIS SYSTEM, FIBRINOLYSIS WITH CHD IN MEN AND WOMEN 40-54 YEARS OLD

As follows from the above review of literature, the following factors are the most informative in assessing changes in the system of hemostasis and fibrinolysis in relation to patients with coronary artery disease: prothrombin index, fibrinogen, soluble fibrin, ethanol test, which allow you to get an idea of the coagulation activity of blood and its readiness for intravascular coagulation; Free heparin, antithrombin Sh, FDPs (fibrinogen degradation products), fibronectin make it possible to assess the anticoagulation readiness of the body.

These parameters were used to assess the state of hemostasis. Fibrinolysis in the population of men and women in Andijan.

Indicators of the hemostasis and fibrinolysis system in the population

The main indicators of hemostasis and fibrinolysis were studied in women and men aged 40 to 54 years. At the young age of 40-44 years, antithrombin-S did not differ from the average level, while at the age of 50-54 years, its decrease from 77.3 to 73.3 ($p< 0.05$) was noted. In contrast, this difference was not statistically significant in women. The difference between men and women was 4.7 per cent (Table 1). 4.1.). In all groups, men tended to have an increase in FDPs. The increase was more pronounced in the 40-44 age group. In women in all age groups, no significant deviations were detected. There was a slight decrease in the ages of 45-49 years, both in men and women (Table 1). 4.2.). In women, this indicator is higher than in men ($p< 0.001$), with the exception of the age group of 50-54 years, where they are almost identical.

As for soluble fibrin (Table 1). 4.3.), its concentration significantly increased with age in men and practically did not change in women. Moreover, it should be noted that in men its minimum concentration was noted at the age of 45-49 years. In the two younger age groups, the level did not differ from each other, although its concentration at the age of 50-54 years increased by 27 mg/dL compared to the group of 45-49 years ($p< 0.01$).

As for the time of thrombin formation (Table 4.4.), in men, the average age levels do not undergo statistically significant differences between the age groups 40-44 and 45-49, although in the older group this indicator decreases from 20.5 to 16.10 ($p< 0.05$) (inversely proportional relationship between the time and the value of thrombin). The latter indicates increased thrombin formation. An increase in thrombin formation in women aged 45-49 years compared to the age of 40-44 years is a shortening of thrombin time by 6.3 seconds ($p< 0.001$), in the older age group there is a tendency to its further decrease.

On average, at the age of 40-54 years, the time of thrombin formation in women is 3.7 seconds higher than in men ($p< 0.01$), although these differences are mainly due to the very large difference during thrombin formation in men and women in the age group of 50-54 years, where it is equal to 7.7 seconds ($p< 0.01$).

Table 4.1. Mean values and major percentiles of antithrombin 111

In men and women aged 40-54 years.

Age	Number of persons	X	M	Percentiles						
				min	5	25	50	75	95	Max
A. Men										
40-44	153	77,25	1,33	35	50	69	78,0	86.0	100	141
45-49	172	75,41	0.91	34	60	70	78,0	83,0	90	148

50-54	232	79,90	0,62	30	61	68	74	80	86	140
40-54	557	75,59	0,53	30	58	69	81,0	92,0	148	145
B. Women										
40-44	131	77,52	1,09	38	59	70,0	78,0	86,0	94	140
45-49	158	72,62	1,33	31	46	66	73,0	80,0	110	134
50-54	112	78,59	1,35	35	61	71,5	78,0	84,0	100	145
40-54	401	76,68	0,74	31	53	69,0	76,0	84,0	100	145

Table 4.2 FDPs **Mean and Major Percentiles**

in men and women aged 40-54 years

Age	**Number of persons**	**X**	**m**	**Percentiles**						
				min	**5**	**25**	**50**	**75**	**95**	**Max**
A. Men										
40-44	154	15,32	1,21	5	5	6,0	10,0	15	50	75
45-49	168	12,35	0,69	5	5	6,0	10,0	15	26	50
50-54	233	13,34	0,62	2	5	7,0	10,0	15	33	54
40-54	555	13,59	0,47	2	5	6,0	10,0	15	49	75
B. Women										
40-44	132	10,97	0,96	4	5	5,0	9,0	15	50	60
45-49	159	9,97	0,79	5	5	8,0	10,0	15	25	75
50-54	114	13,54	1,27	5	5	7,0	10,0	15	50,0	75
40-54	405	11,38	0,57	4	5	7,0	10,0	15	37	75

Table 4.3 SF **Mean Values and Major Percentiles**

In men and women aged 40-54 years

Age	**Number of persons**	**X**	**m**	**Percentiles**						
				min	**5**	**25**	**50**	**75**	**95**	**Max**
A.Men										
40-44	150	9.13	0.56	2	2	5.0	6.0	12	20	40
45-49	165	8,45	0.39	2	4	5.0	6.0	10	20	28
50-54	230	11,16	0.57	0	3	0,6	8.0	13	28	55

40-54	545	9,78	0,31	0	3	5.0	7,0	12	23	55
B.Women										
40-44	129	8,20	0,53	2	2	5.0	6,0	10	20	50
45-49	154	8.90	0,44	1	4	5.0	8,0	12	16	42
50-54	106	9,10	0,79	2	4	5,0	6,0	12,0	22	46
40-54	389	8.72	0,33	1	4	5,0	6,0	12	20	50

Table 4.4 Mean Values and Major Percentiles of Time Thrombin formation in men and women aged 40-54 years

Age	**Number of persons**	**X**	**m**	**Percentiles**						
				min	**5**	**25**	**50**	**75**	**95**	**Max**
A. Men										
40-44	124	18,84	1.31	8,0	11	13	15,5	18,0	39	155
45-49	95	2,48	1,67	5,0	9	13	16,0	21,0	48	108
50-54	83	16,10	1,19	3,0	7	10	14,0	17,0	32	70
40-54	302	18,60	0,82	3,0	9	13	15,0	18,0	47	115
B. Women										
40-44	113	18,81	1,12	0,0	11	13	15,0	2,0	42	86
45-49	106	25,07	1,89	4.0	10	14	18,0	28,0	75	105
50-54	75	23,76	2,30	4,1	8	13	16,0	27,0	70	115
40-54	294	222,33	1.01	4.0	10	13	16,0	24,0	65	115

In all age groups in men, free heparin was reduced, which is confirmed by a statistically significant shortening of heparin time, but the lowest numbers were observed between the ages of 40 and 49 years. The lowest free heparin was found in the youngest group of women aged 40-44 years Mean heparin time levels in women were 1.3 seconds higher than in men. ($p< 0.05$) (Table 4.5)

Table 4.5. Mean values and main percentiles of heparin time in men and women aged 40-54 years

Age	**Number of persons**	**X**	**m**	**Percentiles**						
				min	**5**	**25**	**50**	**75**	**95**	**Max**
A. Men										
40-44	111	5.74	0,41	1	1	3,0	4,0	7.0	14	32

45-49	75	6,97	0,51	0	2	4,0	6,0	9,0	16	22
50-54	78	8,14	0,62	0	3	5,0	7,0	10,0	16	36
40-54	264	6,80	0,29	0	2	4,0	6,0	8,5	15	36
B. Women										
40-44	99	6,02	0,43	0	1	3,0	6,0	8.0	14	28
45-49	72	8,49	0,80	0	1	3,0	7,0	11,0	23	32
50-54	56	11,34	1,73	1	2	5,0	9,0	14,5	25	95
40-54	227	8,11	0,55	0	1	3,0	7.0	10,0	21	95

The prothrombin index in men and women is not subject to age-related changes and is almost the same. (Table 4.6)

Table 4.6. PTI Mean and Major Percentiles

In men and women aged 40-54 years

Age	**Number of persons**	**X**	**m**	**Percentiles**						
				min	**5**	**25**	**50**	**75**	**95**	**Max**
A. Men										
40-44	137	92,58	1,38	32,0	65	86,0	95,0	100,0	114	150
45-49	109	94,96	1,25	33,7	77	90,0	95,0	100,0	116	129
50-54	86	93,33	1,51	43,0	61	90,0	96,0	100,0	110	130
40-54	332	93.55	0,80	32,0	69	88,0	95,0	100,0	111	150
B. Women										
40-44	116	94,43	1,37	25,0	74	88,0	95,0	105,0	114	130
45-49	101	92,20	1,87	27,8	50	88,0	96.0	102,0	116	125
50-54	72	90,44	2,19	10,0	47	86,5	92,0	99,5	110	131
40-54	289	92,66	1,01	10,0	55	88,0	95,0	100,0	115	131

Table 4.7. Fibrinogen Mean Values and Major Percentiles

In men and women aged 40-54 years

Age	**Number of persons**	**X**	**m**	**Percentiles**						
				min	**5**	**25**	**50**	**75**	**95**	**Max**
A.Men										
40-44	132	5,65	0,36	1,10	1,42	2,70	4,35	7,90	14,5	21,9

45-49	93	4,77	0,34	0,73	1,48	2,35	3,90	5,70	11,6	17,7
50-54	79	4,29	0,25	0,27	0,07	2,82	4,20	5,50	8.0	12,6
40-54	304	5,03	0,20	0,27	1,40	2,56	4,20	6,14	12,3	21,9
B.Women										
40-44	109	5,82	0,37	0,27	1,68	3,10	4,76	7,86	13,0	22,3
45-49	115	5,37	0,39	0,10	1,43	2,50	4,10	6,60	13,6	23,6
50-54	69	5,21	0,48	1,40	1,81	2,80	3.81	6,25	11,25	26,4
40-54	293	5,50	0,23	0,10	1,60	1,80	4,10	7,00	13,0	26,4

Table 4.8. Mean values and major percentiles of fibronectin

In men and women aged 40-54 years

Age	Number of persons	X	m	Percentiles						
				min	5	25	50	75	95	Max
A. Men										
40-44	151	406,56	12,5	65,19	200	318	391	480	734	912
45-49	157	409,09	1,6	68,39	165	312	399	494	647	852
50-54	217	394,96	8,5	1,95	210	300	390	480	600	729
40-54	525	402,52	6,11	1,95	200	305	390	483	610	912
B. Women										
40-44	123	375,15	13,37	1,0	153	264	370	456	632	862
45-49	129	398,56	14,16	79,5	142	298	390	504	693	980
50-54	97	386,22	15,64	3,0	99	29	390	470	669	800
40-54	349	386,88	8,27	1,0	135	288	381	476	654	980

As can be seen from Table 4.7, the level of fibrinogen in men decreases with age, and the differences between the 40-44 and 50-54 age groups are 1.36 mg/dL ($p< 0.01$). In women, there is also a tendency to decrease, but the difference is only 0.61 mg/dL ($p< 0.1$). The differences in the average levels of men and women turned out to be almost the same.

Changes in fibronectin in all age groups in men and women, despite visible fluctuations, were statistically insignificant (Table 4.8).

When determining FDPs by the immunochemical method, the absence of age differences in both men and women was found to be similar to the data expressed. It should be noted here that there is a tendency for this indicator to increase in women in all age groups.

We compared the above indicators of the hemostasis and fibrinolysis systems obtained in the studied population with the data obtained by other researchers and with the indicators of their normal values given in the guidelines.

We determined the cut-off points of their distribution series, which allow dividing the population into quartiles for further study of these indicators with the prevalence of CHD in the studied cohorts (Table 4.9)

Relationship of hemostasis and fibrinolysis with the prevalence of coronary artery disease.

Measurement of the relationship between the prevalence of CHD and the level of antithrombin Sh allows us to conclude that with an increase in its level, the number of cases of CHD in the population decreases, and if at its concentration not exceeding 70% (1 quartile of distribution) CHD occurs in 28.0% of the examined men, then in persons with its level exceeding 82.0% (4 quartile) CHD occurred only in 7.9%, i.e. 3.5 times less often ($p< 0.001$).

Table 4.9 Quartile boundary of hemostasis and fibrinolysis indicators

In men and women

Indicators	Quartiles				Norm
	1	2	3	4	
Men					
AT-111	<70	70-75	76-81	82<	80-120%
FDPs	<7	7-10	11-15	15<5-	10mg/dL
SF	<6	6-7	8-12	13<	2-5 mg/dL
TT	<14	14-15	16-18	19<	15-18 sec
HT	<5	5-6	7-8,5	8,5<	7-12 sec
PTI	<89	89-95	96-100	101<	80-100%
FG	<2,57	2,57-4,20	4,21-6,14	6,15<	2-6mg/ml
FN	<306	306-309	310-483	484<	255-405µg/ml
FDPs (IH)	<21,5	21,6-26,5	26,6-31,4	31,5<	5-25µg/ml
Women					
AT-111	<69	69-76	77-84	85<	80-120%
FDPs	<8	8-10	11-15	16<	5-10mg/dL
SF	<5	5-6	7-12	13<	2-5 mg/dL
TT	<14	14-16	17-24	25<	15-18 sec

HT	<4	4-7	8-10	11<	7-12sec
PTI	<89	89-95	96-100	101<	80-1--%
FG	<2,80	2,80-4.0	4,11-7,0	7,12<	2-6mg/ml
FN	<288	288-381	382-476	477<	255-406μ/ml
FDPs (IH)	<20,6	20,6-26,8	26,9-33,8	33,9<	5-25μg/L

A similar pattern was observed in women, with even greater differences. With a low level of **antithrombin III**, CHD occurs 7.2 times more often than with a high level ($p< 0.001$). The analysis of the relationship between SF and FDPs with the prevalence of CHD was carried out taking into account their correlation with each other. The data obtained indicate that the absolute predominance of SF over FDPs is accompanied by an increase in the number of CHD cases in men and women from 1 to 3 and 4 quartiles (Fig. 1). 4.2. and 4.3.)

An analysis of the relationship between an inadequate limited increase in FDPs content in comparison with an increased SF and the prevalence of CHD showed (Fig. 4.2) that in men the number of CHD cases increased from the first to the fourth quartile, where the number of CHD cases was 7.4 times higher than the number of cases in the first quartile ($p< 0.001$).

In the female, the same pattern was observed, although the differences between the first and fourth quartiles were 10.7 times higher ($p< 0.001$). An inappropriately small increase in FDPs in patients with an increase in the CHD clinic is obviously a sign of insufficiency of fibrinolysis activity, taking into account the increase in hypercoagulable activity in this group of patients.

The prevalence of CHD also changes with an increase in the concentration of soluble fibrin. There was also an increase in the number of CHD cases from the first to the fourth quartile. In men, the number of cases increased by 5 times, and in women by 6 times ($p< 0.001$).

When considering the relationship between the prevalence of CHD and the time of thrombosis, a close relationship is revealed, i.e., the shorter this time, the higher the number of cases of CHD. In men, the maximum number of cases was observed in the group where the time of thrombin formation did not exceed 14 seconds (1 quartile) By the third quartile, the number of cases decreased by 4.5 times ($p< 0.001$), after which it increased again to 18.9% (there was an inverse proportional relationship between the duration of thrombin time and thrombosis, i.e., the shorter the time, the higher the thrombus formation)

The same pattern was repeated in women, who had 1.5 times fewer cases of CHD in the third quartile than in the fourth, although the increase in the number of cases in the fourth quartile compared to the third was only 3%. It was noted that, with the exception of the first quartile, CHD was significantly more common in women than in men.

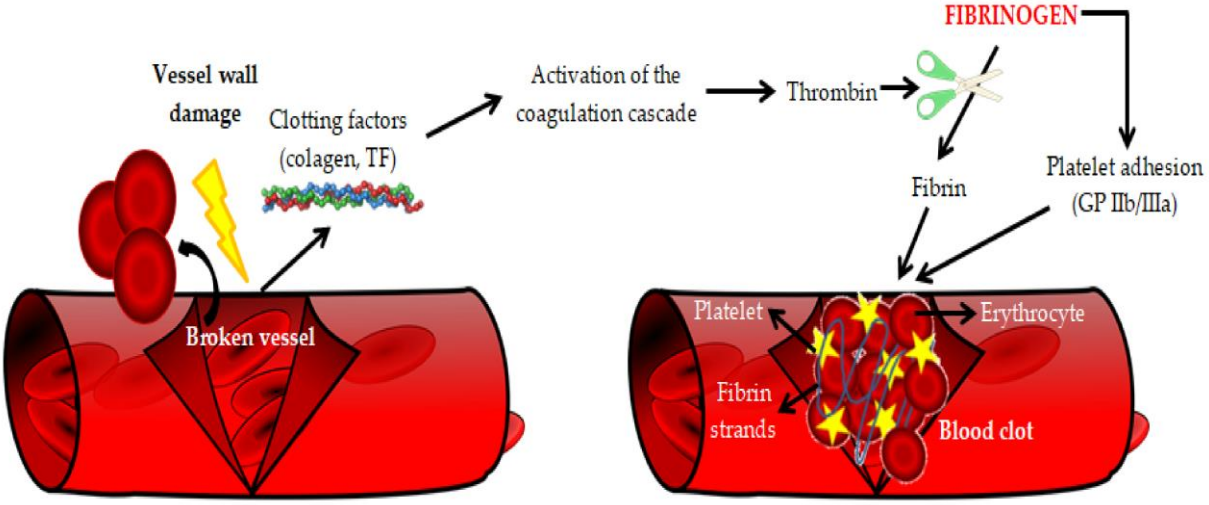
As for free heparin, a linear increase in the incidence of CHD was observed in both men and women with a decrease in its concentration, and if at its normal concentrations CHD occurred in 19.1% of the examined, then at low concentrations in 30.3% ($p< 0.001$). To a large extent, the prothrombin index is also associated with the prevalence of coronary artery disease. In men, CHD was found in 11.1% of the examined patients with low CHD values (Fig. 4.6), while in 35.7% of men with high CHD values, i.e. 3.2 times more often ($p< 0.001$). The differences in the prevalence of CHD in women in similar comparison groups are somewhat smaller, although also highly significant. However, it should also be noted that at all levels of PTI, CHD in women is more common than at low values, these differences reach the greatest value.

As for the ethanol sample (Fig. 4.7), the difference in the value of this indicator upwards between groups 1 and 3 was 7.3 times in men and 4.9 times in women ($p< 0.001$). At any values of the sample, the incidence of CHD in women was higher than in men, but in the first group, CHD in women was 1.7 times more common, and in the third group it was 1.2 times more common than in men.

Differences in the prevalence of CHD at different levels of fibrinogen were also very significant (Fig. 4.8). With the increase in its level, the number of cases of CHD increased from the first to the fourth quartile in men by 7.8 times, and in women by 1.8 times. The absence of a significant increase in the content of fibrinogen in the fourth quartile compared to the third is obviously due to the presence of latent coagulopathy of consumption, especially since it coincides with the similar dynamics of the SF ethanol test.

With an increase in the level of fibronectin in men, there was an increase in the prevalence of CHD from 13.7% in the first quartile to 24.4 in the third, i.e. 1.8 times (Fig. 4.9). In women, these differences are slightly higher, and the maximum number of cases is also in the third quartile. In both cases, in the fourth quartile, where fibronectin was higher, there was a slight decrease in the number of CHD cases. The latter does not preclude its protective role.

Comparing the data obtained by us with the data of the control group, it was concluded that 50% of the results obtained were within the range of the FDPs norm from 5 to 10 mg/dL, while in the second half of the examined, both men and women, this indicator was above 10, i.e. above the generally accepted norm. When comparing the content of **AT-III** with the accepted norms, it can be seen that more than 50% of the examined have this indicator below 80, i.e. below the norm, and only in 20-25% of the examined this indicator is within the normal value.


FIBRINOGEN
Vessel wall damage
Clotting factors (colagen, TF)
Activation of the coagulation cascade
Thrombin
Fibrin
Platelet adhesion (GP IIb/IIIa)
Broken vessel
Platelet
Erythrocyte
Fibrin strands
Blood clot

WORLD HEART FEDERATION

CARDIOVASCULAR DISEASE

THE WORLD'S NUMBER 1 KILLER

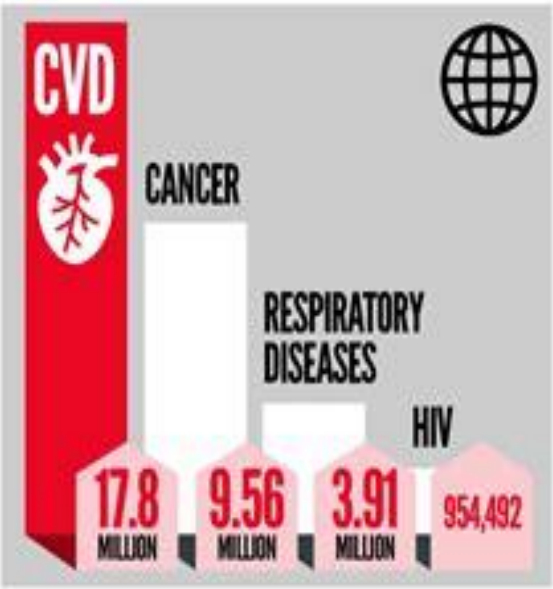
Cardiovascular diseases are a group of disorders of the heart and blood vessels, commonly referred to as **heart disease** and **stroke**.

17.8 MILLION deaths every year from CVD

31% of all global deaths

>75% of CVD deaths take place in low- and middle-income countries

GLOBAL CAUSES OF DEATH



RISK FACTORS FOR CVD

- High Blood Pressure
- Unhealthy Diet
- High Cholesterol
- Diabetes
- Overweight & Obesity
- Tobacco
- Air Pollution
- Kidney Disease
- Physical Inactivity
- Harmful use of alcohol

Sources: World Health Organization; IHME, Global Burden of Disease

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/worldheartfederation
/worldheartfed

Heart Disease

Heart disease includes any disorder of the heart and affects millions of Americans every year, yet it is highly preventable by following a healthy lifestyle.

It is the number one cause of death in the U.S., accounting for 36% of deaths annually.

In 2010, heart disease will cost us an estimated $316.4 billion in health care, medicine and lost productivity.

COMMON RISK FACTORS FOR HEART DISEASE INCLUDE:

Рис. 4.6

TO SCREEN FOR RISK FACTORS, HAVE YOUR DOCTOR:

- Test your blood pressure with a pressure cuff
- Test your blood cholesterol level
- Compute/discuss your Body Mass Index (BMI)

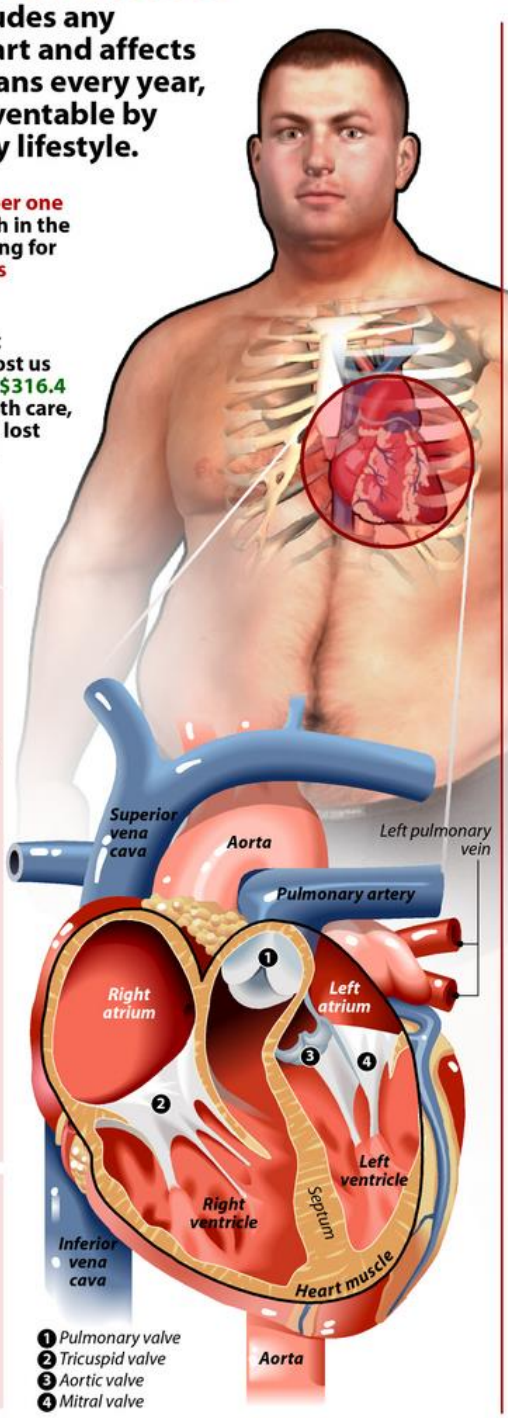
HOW TO LOWER YOUR RISK

- Quit smoking
- Exercise
- Eat your fruits and vegetables
- Avoid salt and fatty foods
- Limit alcohol
- Get regular medical exams

And, if applicable:

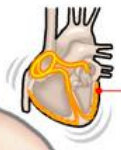
- Take blood-pressure-lowering meds (for people wit re)
- M gar lev

Рис. 4.7

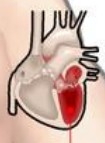


TYPES OF HEART DISEASE

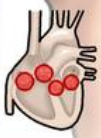
Coronary heart disease
Blocked or clogged arteries limit blood flow to the heart and starving it of oxygen and nutrients.



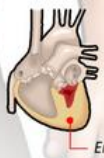
Arrhythmia
The heart beats irregularly.



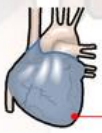
Heart failure
The heart can't pump as powerfully as it needs to in order to supply the body with oxygen and nutrients, causing the heart muscles to overwork and weaken.



Heart valve disease
One of more of the hearts' valves — which control blood flow into and out of the heart — doesn't work.



Cardiomyopathy
An enlarged or abnormally stiff or thick heart, causing the heart to pump weaker than normal and sometimes leading to heart failure or arrhythmia.



Pericarditis
An inflammation of one or more layers of the pericardium, a thin membrane that lines the heart.

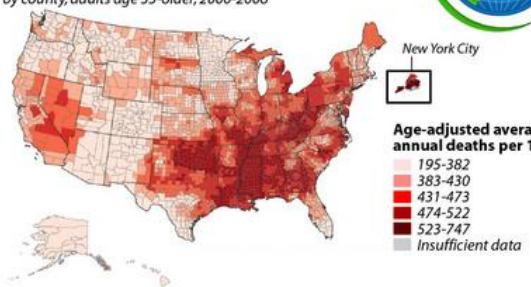
Aorta disease
A portion of the aortic wall weakens and balloons out, forming an aneurysm.

Vascular disease
Heart disease is often related to diseases of the circulatory system, including arteries, veins and lymph vessels, or blood disorders.

FAST FACTS

- Heart disease is the **leading cause of death** in the U.S.
- It is the **leading cause** for **both men and women,** and the deaths are **split evenly** across gender.
- Every **34 seconds** in the U.S., someone has a **heart attack.** Every **minute,** someone dies from **heart disease.**
- About **79 million** Americans have some form of **cardiovascular disease.**

Heart disease death rates in the U.S.
by county, adults age 35-older, 2000-2006



SOURCE: National Vital Statistics System and U.S. Census Bureau

INFO GRAPHIC WORLD

SOURCES: American Heart Association; WebMD; Centers for Disease Control and Prevention; National Heart Lung and Blood Institute

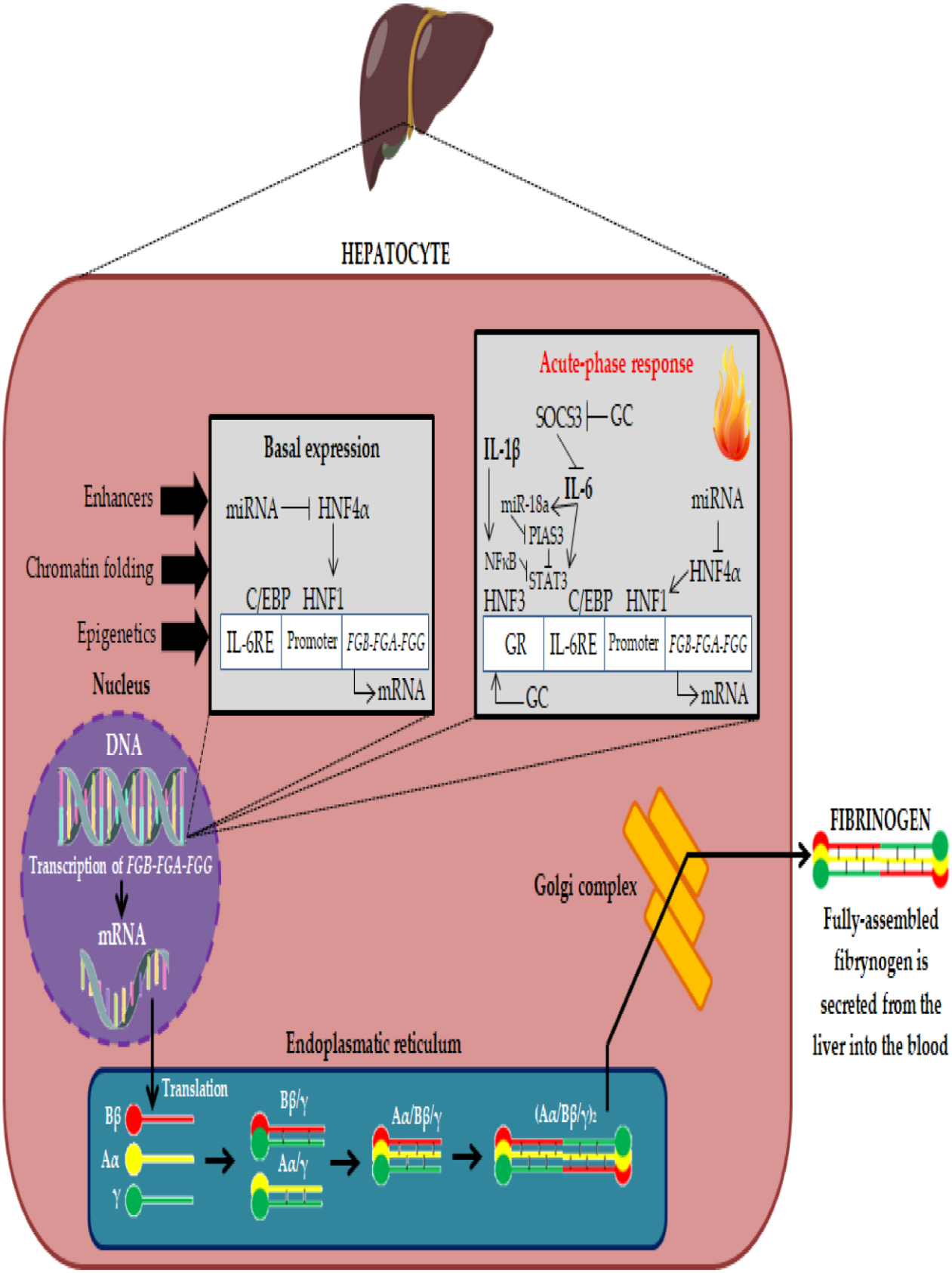

HEPATOCYTE
Basal expression
Enhancers
Chromatin folding
Epigenetics
Nucleus
miRNA
HNF4α
C/EBP
HNF1
IL-6RE
Promoter
FGB-FGA-FGG
mRNA
Acute-phase response
SOCS3
GC
IL-1β
IL-6
miR-18a
PIAS3
NFκB
STAT3
HNF3
GR
DNA
Transcription of FGB-FGA-FGG
mRNA
Golgi complex
FIBRINOGEN
Fully-assembled fibrynogen is secreted from the liver into the blood
Endoplasmatic reticulum
Translation
Bβ
Aα
γ
Bβ/γ
Aα/γ
Aα/Bβ/γ
(Aα/Bβ/γ)2

Table 4.10 Low, Medium and High Risk of CHD for Hemostasis and Fibrinolysis

Indicators	Risk Boundaries		
	Low	**Average**	**High**
Men			
AT-111	**82+**	**76-81**	<75
FDPs	**5-6**	**7-10**	**11+**
SF	**2-5**	**6-7**	**8-12**
TT	**16+**	**14-15**	<14
HT	<7	**-**	**7+**
FG	<4,2	**4,3-6,1**	**6,2+**
FN	<390	**-**	**390+**
FDPs (IH)	<21,5	**21,5-26,5**	**26,6+**
Women			
AT-111	**84+**	**-**	<84
FDPs	**4-7**	**7-10**	**11+**
SF	**2-4**	**5-6**	**7-12**
TT	**17+**	**14-16**	<14
HT	<7	**-**	**7+**
FG	<4,1	**4,2-5,9**	**7+**
FN	<382	**-**	**382+**
FDPs (IH)	<20,6	**-**	**20,6+**

Assessing the association of this indicator with the prevalence of CHD, it was found that a sharp decrease in the number of CHD cases was observed in individuals with **AT-III** levels above 81% in men and 77% in women. Less than 25 per cent of men and about 50 per cent of women fall within these levels. These limits are considered acceptable for assessing the level of the minimum risk of CHD (Table 4.10).

The normal range of soluble fibrin is considered to be the limit of 2 to 5 mg/dL. According to our data, within these limits, this indicator occurs in 25% of people with its lowest level. However, as can be seen from the same figure, CHD is more common among individuals with a higher level of SF, starting with its concentration in the range of 6-7 mg/dL in men and 5-6 in women (Table 4.10)

As can be seen from Table 4.9. The normal time of thrombin formation is 15-18 seconds. According to our data, in 50% of the examined, these values were below 15 seconds. CHD was

most common among individuals whose thrombus formation time was less than 14 seconds, both in men and women. The most favorable is the time of thrombin formation from 15 to 18 seconds in men, from 15 to 24 seconds in women (Fig. 4.4) Based on this, we propose the following limits for determining the risk level for this indicator: high < 14 seconds, medium 14-15 seconds, and low 15 seconds and higher (Table 4.10)

When assessing the free heparin index by quartile distribution, free heparin tended to decrease everywhere, and this allows it to be attributed to the risk factors for CHD (Table 4.10) Comparing the data with the proposed limits of the PTI norm, it should be noted that in 75% of the surveyed patients this indicator had this indicator within the specified values in both men and women. However, considering these results from the point of view of its relationship with coronary artery disease, it should be noted that the minimum number of diseases occurs in individuals where the PTI is below 89% (Fig. 4.6), and then there is an equal increase in the number of cases with CHD. Therefore, from our point of view, it is reasonable to consider that persons with PTI from 90 to 100 and above 100 are tall (Table 4.10)

Fibrinogen within the suggested norm in our population was found in 75% of the examined (Fig. 4.7). The prevalence of CHD within these boundaries is not equal. Thus, among people with a level of up to 4.2, it is very low, and at the same time from 4.2 to 6.1 in men and up to 7 in women, it is the maximum.

According to the data obtained, it is reasonable to classify individuals with a fibrinogen level of up to 4.2 as a low-risk group, with a level of 4.3-6.0 as medium and above 7-high.

The level of fibronectin does not change significantly in a significant group of patients. A slight increase in the content of fibronectin coincides with an increase in the prevalence of coronary artery disease, up to the third quartile (in the fourth quartile it decreases), which should be attributed to the appearance of a persistent protective reaction of the body aimed at mitigating the signs of hypercoagulation (Table 4.10)

It follows from the presented data that in both men and women in all quartiles FDPs does not differ significantly from the norm, with the exception of the 4th quartile, where there is a moderate increase. Given that FDPs is the result of soluble fibrin, this value should be estimated in relation to the latter. As shown in Table 4.10, the SF had a certain tendency to increase from 1 to 4 quartiles, both among men and women.

Thus, in the characteristics of these two indicators, an imbalance in the form of increased fibrin formation and relatively low fibrin destruction was revealed. The upward ratio of SF and FDPs should be attributed to the high risk factor of coronary artery disease.

Thus, having considered the levels of hemostasis and fibrinolysis indicators as a whole, we have assessed these indicators in three age groups of men and women, established their average values and the boundaries of the quartiles of distribution. Further, a comparative assessment of the relationship between each of them and the prevalence of CHD was carried out and the boundaries of groups with different levels of risk of CHD were determined, which will allow doctors to assess the patient's condition along with the clinical picture, taking into account these factors.

Prognostic significance of hemostasis and fibrinolysis indicators.

We made a final assessment of the causal relationship between the studied risk factors and the occurrence of new fatal and non-fatal cases of coronary artery disease. A prospective assessment of the following hemostasiological parameters was carried out:

Antithrombin III. As shown in Figure 4.10, the number of new cases of CHD in men in the absence of a decrease in the level of **AT- III** tends to decrease, and in the fourth quartile the number of new cases was 2.0 times less than in the first and 2.2 times less than in the second.

In women, a similar pattern was observed and there was a significant decrease in the number of new cases in the second and fourth quartiles.

FDPs**.As** FDPs levels increase, there is an increase in the number of new cases from the first to the third and fourth quartiles, in both males and females (Figure 4.11). As we indicated above, the assessment of this indicator is possible in relation to the content of soluble fibrin and fibrinogen.

RUSSIA. As can be seen from Fig. 4.12. The Russian Federation has a clear tendency to increase from the first to the fourth quartile for men and from the first to the second and third quartiles for women, remaining in the fourth quartile almost at the same level.

When comparing the values of FDPs and SF, the following was revealed: the apparent increase in the FDPs content did not go beyond the norm and in most cases the SF content statistically significantly increased, which, as mentioned above, is a reflection of an imbalance in the characteristics of these indicators and indicates the presence of increased fibrin formation with neodequatively low fibrin destruction.

The data obtained by us in a prospective study allow us to recommend an assessment of the ratio of SF to FDPs as a prognostic feature with a noticeable predominance of the former.

Thrombin time. When analyzing the thrombin formation indicator by thrombin time, the following was established: an increasing increase in thrombin formation, a manifested shortening of thrombin time corresponded to the occurrence of new cases of CHD increasing

from the first to the third quartile, where the number of new cases of CHD was 12 times higher than in the first quartile. In women, the pattern was somewhat weaker, but similar (Figure 4.13) When co[illegible]lata with the picture obtained from the study of the prevalence of CHD in both m[illegible] the dependence curves are absolutely identical (Fig. 4.4), which makes it possible to consider this indicator as a prognostic factor.

Рис. 4.9

However, it should be noted once again that the most unfavorable level is below 14-16.

Free heparin. The association of free heparin with the occurrence of new cases of CHD is also of interest. In both men and women, there is an increase in their number with a decrease in this indicator. Given that we have already noted a similar relationship between this indicator and the prevalence of coronary artery disease, we can recommend it as a prognostic factor for hypercoagulability. In the prognosis of coronary artery disease. (Fig. 4.14)

Prothrombin index. As can be seen from the data presented in Figure 4.15, there is an increase in new cases of CHD in both men and women.

Ethanol test. From the data presented, it follows that in both men and women, there is a direct relationship between the increase in the ethanologic test and the increase in new cases of coronary artery disease.

Fibrinogen. When analyzing the data, it can be seen that there is a close relationship between the content of fibrinogen and the increase in new cases of CHD in both men and women. The maximum number of cases falls on the third and fourth quarters in men and women, where the content of fibrinogen in men increases by 6 times compared to the first quarter, in women by 4 times. Slight deviations in fibrinogen levels in the fourth quarter may be associated with an increase in the clinical severity of coronary artery disease. the occurrence of coagulopathy of consumption with the conversion of fibrinogen to fibrin. Moreover, these patients were found to have an increased content of SF and the absence of an adequate increase in FDPs.

Thus, an increasing increase in fibrinogen content in patients with progressive CHD is a highly informative prognostic unfavorable sign. However, a comprehensive assessment of this indicator is carried out simultaneously with the characteristics of the FDPs and the SF. Taking into account the critical picture of the disease, it seems to be the most valuable and significant. The latter will make it possible to ascertain not only the signs of hypercoagulation, but also the transition in the quantitative growth of the latter into a qualitatively new state (DIC syndrome) - fibrinogen into fibrin.

Fibronectin. Dynamic assessment of fibronectin content shows that it tends to increase slightly, both among women and men, in parallel with the emergence of new cases of CHD in the fourth

quartile, where the amount of fibronectin with the largest number of new cases of CHD decreases, which indicates a possible protective function of fibronectin.

Thus, it can be said that in the univariate analysis, the clearest dependencies between the occurrence of new cases of CHD and the indications of hemostasis were registered in relation to the thrombin time of fibrinogen **AT III**and the ratio between SF and FDPs, which is a device for increasing blood coagulation in the form of accelerated thrombin – phyrin formation with reduced activity of the anticoagulation system.

MICROCIRCULATION INDICATORS, THEIR CHARACTERISTICS AND RELATION TO CHD

Indicators of microcirculation in the population

In recent years, the study of the condition of the MC by microscopy of the vessels of the bulbar conjunctiva in patients with various pathologies of the internal organs has been widely used. This method is more sensitive and highly informative compared to the study of the fundus. Many researchers believe that there are no specific changes in the BFI in most pathological processes. However, the assessment of the results of changes in the MC makes it possible to identify a number of its features that are most characteristic of a particular pathology and to judge the direction of pathological changes in transcapillary metabolism and changes in the vessels of the heart, as well as the degree of its severity, which makes it possible to increase its ability to diagnose CHD in the clinic.

It is generally recognized that MC changes play an important role in the pathogenesis of CHD in various vascular regions, MC disorders are detected in the form of changes in tissue blood flow, capillary permeability, microhemorheology, microthrombosis, and microvascular architectonics.

Assessment of BFI changes was carried out using XL-2B with a magnification of 30 to 60 times and consisted of the study of vascular, intravascular and perivascular changes, both venous and capillary and arteriole beds of the microcirculatory system. In the summary assessment of the indicators, indices were compiled (ICI – index of vascular changes, BFI – intravascular index of blood flow, FAI – index of perivascular changes, SI – total index) There is a direct proportional relationship between the value of the indices and the degree of impairment of the MC system.

Microcirculation indicators and their relationship with CHD were studied among the male and female population aged 40-54 years. Our findings suggest that FAI in men increases with age.

Table 6. Mean values of FAI in age-sex national groups

Age	Indigenous		Non-indigenous		Altogether	
	M	m	M	m	M	m
Men						
40-44	0,73	0,05	0,76	0,06	0,61	0,10
45-49	0,88	0,05	0,89	0,07	0,67	0,11
50-54	0,94	0,04	0,95	0,06	0,87	0,09
Women						
40-44	0,99	0,07	0,96	0,08	1,09	0,18
45-49	0,98	0,06	1,00	0,08	0,95	0,10
50-54	1,06	0,08	1,04	0,10	1,09	0,12

In both the indigenous and non-indigenous populations, the average level at the age of 50-54 is 1.3-1.4 times higher than at the age of 40-44 years ($p< 0.01$) (Table 6).

As for the ASI, there is a clear increase in this indicator in men of indigenous nationality, in the older age group its level increases by 17% compared to the younger one ($p< 0.01$) (Table 7) In indigenous women, there is also a clear increase in this indicator with age, from 8.39 in the younger group to 10.2 in the older group ($p< 0.01$). At that time, ethnic differences were not noticeable among non-indigenous women.

Table 7. Mean values of ASI in age-sex national groups

Age	Indigenous		Non-indigenous		Altogether	
	M	m	M	m	M	m
Men						
40-44	8,52	0,25	8,47	0,28	9,20	0,61
45-49	8,96	0,24	8,90	0,30	9,29	0,49
50-54	9,91	0,25	9,95	0,32	9,28	0,38
Women						
40-44	8,69	0,29	8,39	0,31	9,96	0,76
45-49	9,50	0,26	9,33	0,35	9,715	0,40
50-54	10,22	0,40	10,20	0,40	10,25	0,65

A similar picture is observed with regard to the BFI in indigenous men, this index increases with age from 2.69 to 3.15 ($p< 0.01$), while in non-natives it remains consistently high and in the younger age group it is significantly higher than in the indigenous population ($p< 0.05$) (Table 8)

Table 8. Mean values of BFI **in age-sex national groups**

Age	Indigenous M	m	Non-indigenous M	m	Altogether M	m
Men						
40-44	2,77	0,16	2,69	0,18	3,27	0,15
45-49	2,94	0,16	2,80	0,19	3,21	0,36
50-54	3,32	0,15	3,15	0,19	3,28	0,26
Women						
40-44	3,05	0,19	2,86	0,19	3,96	0,60
45-49	3,57	0,18	3,44	0,25	3,73	0,27
50-54	3,76	0,22	3,58	0,27	4,04	0,37

In the case of women, even in the absence of age-related changes in the non-indigenous population, there is a clear increase with the age of the indigenous population.

Microcirculation and CHD prevalence

The data obtained by us clearly showed that with an increase in SI (total index), there is an increase in the number of CHD cases (Fig. 5.1). In men in the fourth quartile, the prevalence of CHD is 83.0 times higher than in the first, and in women these differences are 19.8 times. Therefore, it can be said with certainty that the presence of pronounced changes in SI to a large extent takes place in patients with coronary artery disease.

A clear link was also observed between ASI and CHD (Fig. 5. 2.).

In men, the difference between the first and fourth quartiles is 12.7 times, while in women these differences are 5.1 times. The most distinct elements of ASI influencing the prevalence of CHD were the following: a pronounced decrease in the number of arterioles, a significant narrowing and pronounced irregularity of their lumen, fusiform aneurysms, irregularity of the lumen and multiple fusiform aneurysms of venules, an increase in their tortuosity, the presence of a zone of emptiness in the capillary bed, a pronounced narrowing of arteriaol precapillaries, and dilation of venous postcapillaries. The link between BFI and the prevalence of CHD is no less clear. (Fig. 5.3).

In men from the first to the fourth group, the number of cases increases by 18 times, and in women by 15 times. The strongest element of ASI was the emptying of capillaries (a decrease in the number of capillaries in the field of vision). Other elements were closely related to this indicator with high statistical significance. After taking into account the strongest element, the following independent contribution to the prevalence of CHD remain: venule dilation, irregular capillary arcade pattern, constriction of precapillaries and dilation of postcapillaries, slowing of blood flow in arterioles, deposition of cholesterol in perivascular tissue. From the presented

characteristics of microcirculation, it follows that in CHD there is a significant disturbance both in the vascular wall itself and in the blood flow, as well as perivascular deposits, which were highly correlated with the spread of CHD. Thus, the generally accepted opinion that CHD is based on atherosclerosis of the large coronary vessels can be supplemented by the presence of an organic lesion of the microcirculatory bed responsible for transcapillary exchange.

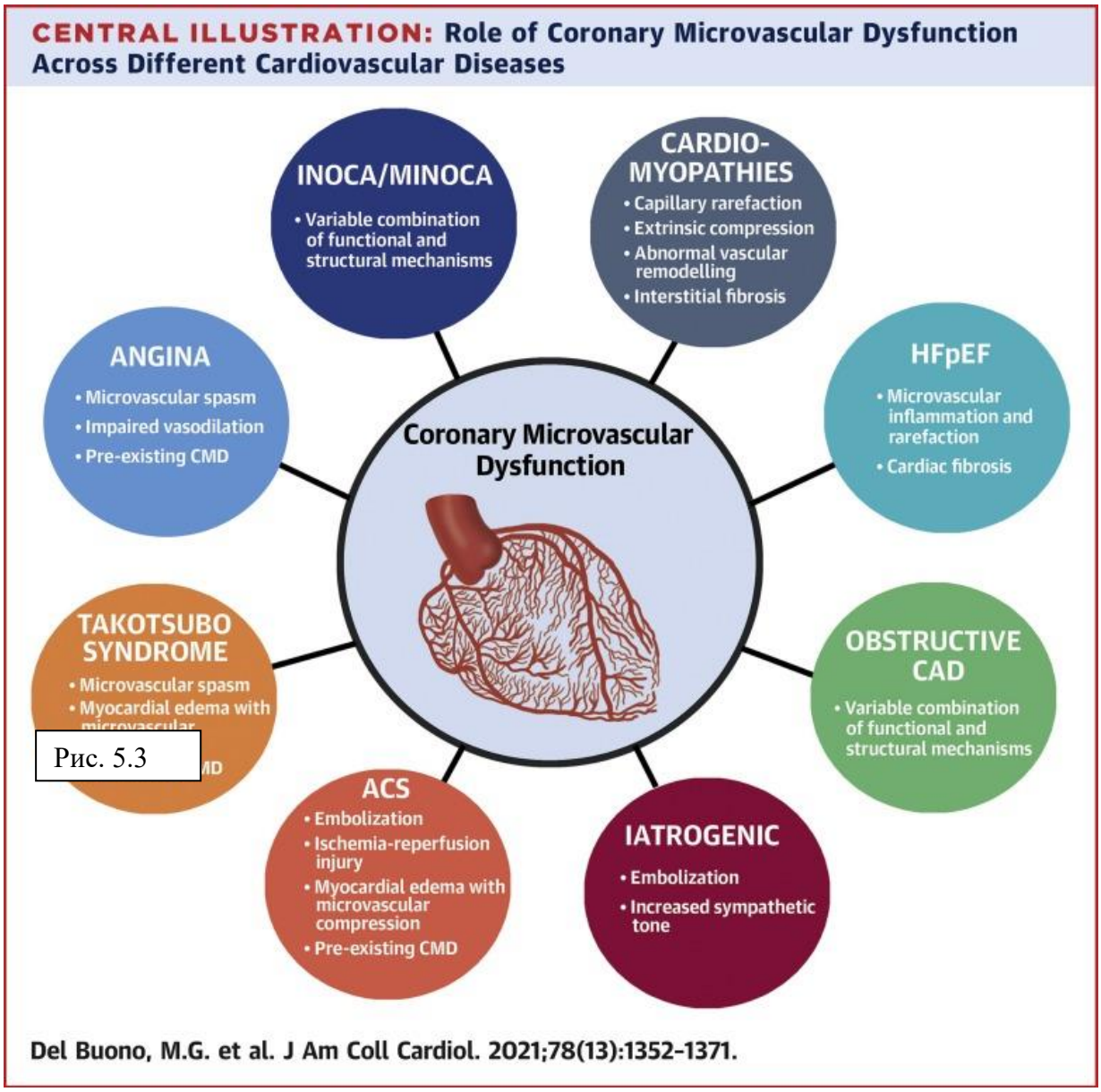


Рис. 5.3

Microcirculation indicators and new cases of CHD

As in the assessment of **hemocoagulation** rates, both fatal and non-fatal cases of CHD were included in the number of new cases.

Our data suggest that the number of new cases of CHD is weakly related to the level of FAI in men and women. In men, there was an increase in the number of new cases in the fourth quartile compared to the first, while the number of new cases decreased in the second. In women,

on the contrary, the number of new cases decreased. As for SI, we did not register any new cases of CHD in men in the first group, and almost 10 in the fourth group. In women, the number of new cases from the first to the fourth group increased by 4.7 times.

Figure 5.4 shows that an increase in ASI is accompanied by an increase in the number of new cases in both men and women by 4.1 and 5.7 times, respectively ($p< 0.05$). It should be noted, however, that the clearest link was between the occurrence of new cases and the magnitude of BFI. In men, no new cases of CHD were registered in the first group, and in the fourth group they reached 11.8 ($p< 0.001$). In women in the fourth group, the number of new cases was 14 times higher than in the first group ($p< 0.001$). A special analysis of this association among those who died from CHD yielded similar data.

Thus, it is evident from the above that all the MC indicators selected by us can be used as prognostic indices, but the clearest correlation can be traced between the number of new cases and BFI, which can be recommended as one of the leading indicators in the survey program during preventive examinations of the population, in order to identify the preclinical stage of coronary artery disease.

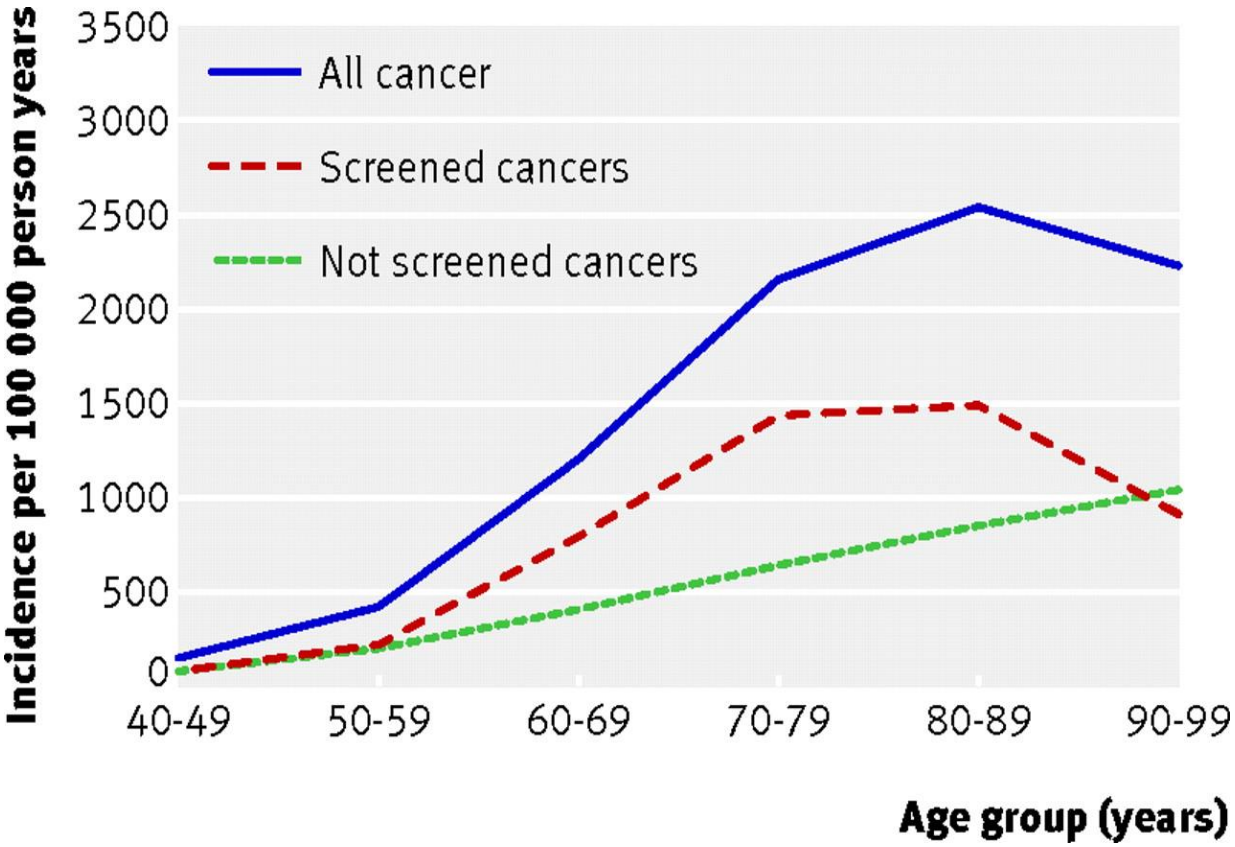
Combined effect of the main risk factors and microcirculation indicators on the prevalence of CHD

Of considerable interest is the combined effect on the prevalence of CHD of traditional risk factors and previously unknown in the form of microcirculation indicators. The assessment of microcirculation consisted of the characterization of vascular (ASI), intravascular (blood flow index - BFI) and perivascular (III) changes. In the course of the study, it was evident that (Fig. 5.8) the addition of a pathological (greater than 12) ASI value to any set of risk factors significantly increased the prevalence of CHD. For example, in the case where elevated ASI was the only factor, the number of registered CHD cases was 3.6 times higher than in the group without a single risk factor ($p< 0.01$). The combination of DLP with increased ASI increased the prevalence of CHD by 2.4 times ($p < 0.05$). A similar picture was observed for other indicators (Fig. 5. 8).

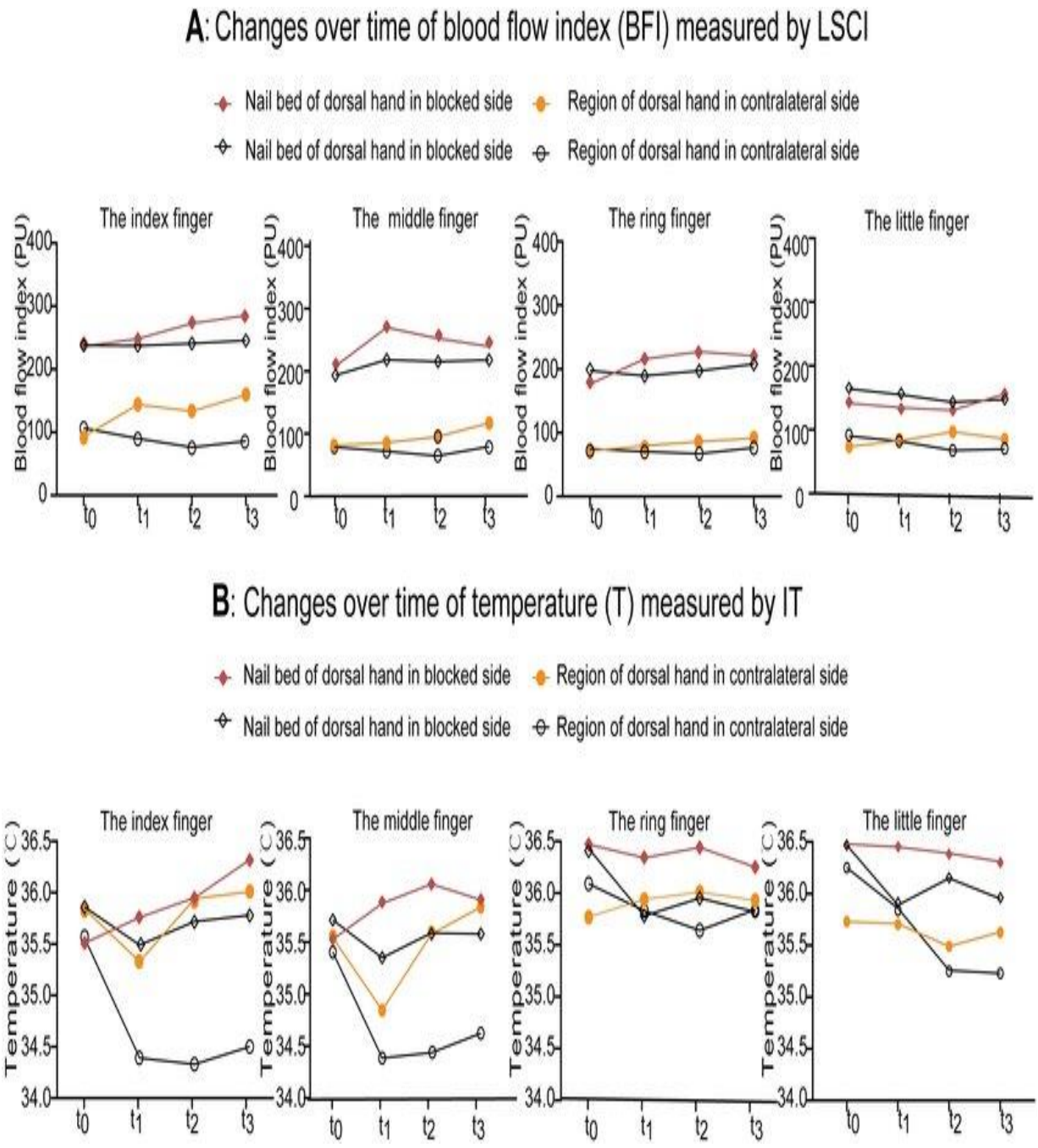
The combination of elevated BFI with other risk factors indicated an increased association of any of the risk factors with the prevalence of CHD. Even in the case where this factor was the only one, CHD was 6 times more common than among individuals without any of them ($p< 0.01$). In cases where this factor was combined with others, CHD was even more common. This was especially pronounced when increased BFI was combined with DLP (dyslipoproteinemia), both alone and in combination with BMI (overweight) ($p< 0.01$)

In the case of SI, its high values, combined with other factors, also correspond to a significant increase in the number of CHD cases (Figure 10). If in the group where SI is greater than 18, the incidence of CHD was 6.7 times higher than among persons without risk factors ($p< 0.01$) and amounted to 50.0%, where SI was combined with DLP and BMI, CHD was already found in 85.7% of the examined, which exceeded the number of cases in the group without increased SI by 4.7 times ($p< 0.01$).

Thus, the study once again confirmed the importance of microcirculation system indicators as risk factors for coronary artery disease, allowing to improve its diagnosis, both at the preclinical stage, and to choose the most adequate approaches to secondary prevention of this disease.



Picture. 10



The combined effect of ASI and **BFI** with the main risk factors on the prevalence of CHD is shown

CHANGES IN THE LEVEL OF THE MAIN RISK FACTORS AND INDICATORS OF HEMOSTASIS AND MICROCIRCULATION IN THE INTERVENTION GROUP AND IN THE CONTROL GROUP

The revealed disorders in the system of hemostasis, fibrinolysis and microcirculation in patients with CHD put forward the need for therapeutic intervention. For this purpose, two groups were created, equivalent in terms of clinical characteristics of the disease and age. The intervention group of 89 people received aspirin disaggregation therapy 0.25 once daily for two months. The comparison group (71 controls) did not receive treatment. Patients who had elevated blood pressure continued to take antihypertensive drugs in both the control and intervention groups.

The intervention group was under regular observation and, according to indications, they were given fasting days, a low-salt diet, fluid restriction, sedative therapy to regulate mental status, and an even distribution of physical and mental load and rest was recommended.

Comparing the data of the two measurements in the comparison group and in the intervention group, we found that in men SBP in the control group almost did not change, while in the intervention group SBP decreased, while in the control group it practically did not change. In the intervention group, a positive trend was also revealed in the characteristics of clinical symptoms of the disease. This was manifested by an increase in performance, a decrease in headaches and shortness of breath, an improvement in sleep, a decrease in noise in the head, the disappearance of flickering flies in front of the eyes, and an improvement in general well-being.

A dynamic study of lipid metabolism in the form of determining the content of cholesterol, alpha lipoproteins, triglycerides did not reveal a significant difference in any of these parameters in the comparison groups, control and intervention. The therapy was not aimed at changing these parameters.

Indicators of hemostasis and fibrinolysis

As for the indicators of hemostasis and fibrinolysis, all of them have undergone significant changes under the influence of the therapy. Antithrombin **III** in the male placement group increased by 6.4% ($p< 0.001$), while in the control group its level decreased by 2.39 ($p< 0.1$) (Fig. 6.1). In women in the intervention group, it increased by 8.8% ($p< 0.001$), while in the control group it decreased by 6.4% ($p< 0.001$) (Fig. 6.2)

FDPs decreased by 4.24 ($p< 0.01$) in the intervention group in men and increased by 1.55 in the control group ($p< 0.001$).

The same pattern was observed in women, but the degree of decline in the intervention group was slightly lower, and the increase in the control group was higher than in men.

Soluble fibrin decreased by 2.37 in the intervention group in men ($p< 0.001$), while in the control group it significantly increased by 1.03. In women, this decrease was 1.86 ($p< 0.001$) in the intervention group, while in the control group there was a significant (1.56) increase in this indicator ($p< 0.001$). As for the time of thrombus formation, it lengthened by 4.3 seconds in men and by 3.2 seconds in women in the intervention group ($p< 0.001$), while in the control groups, on the contrary, it significantly decreased ($p< 0.001$)

There is an inversely proportional relationship between the time of thrombogenesis and thrombogenesis, i.e. the data obtained indicate a decrease in thrombogenesis in the intervention group.

A similar pattern was revealed in the dynamics of free heparin. Free heparin ($p< 0.001$) also increases under the influence of the proposed therapy, while in the control group it decreases.

The prothrombin index decreases in both men and women, by 5.4 and 7.13, respectively ($p< 0.001$). In the control group, there is a significant increase in this indicator ($p< 0.001$).
Fibrinogen concentrations in the intervention group decreased in both men and women ($p< 0.001$), but while in men this decrease was 82.9% of baseline, in women it decreased by 27.7% to 5.93.

A slight decrease was also observed for fibronectin, which in the intervention group decreased by 2.4% from baseline in men and by 2.1 in women ($p< 0.001$). At that time, in the control group, there were slight fluctuations in this indicator in both men and women. ($p< 0.01$). FDPs determined by immunochemical method decreased in the intervention group by 17.9% in men and by 26.6% in women ($p< 0.001$). At the same time, in the control group, we observe a slight increase in this indicator. The simultaneous decrease in SF, fibrinogen, and FDPs should be attributed to the indicator of the decrease in latent DIC.

Thus, under the influence of the prophylactic treatment, the indicators of FDPs, SF, PTI, fibrinogen, fibronectin decreased. At the same time, AT-**III** and free heparin increased, and the time of thrombus formation was prolonged. In the control group, there were no positive changes in hemostasis with some deterioration in a number of them.

Thus, our data allow us to conclude that the therapy had a positive effect in both men and women, although the degree of these changes was not the same in them.

The latter consists in a statistically significant limitation of latent increased thrombino-fibro formation (DIC) due to a decrease in both the procoagulation activity of plasma and due to the activation of coagulation inhibitors (AT-**III**, fibrinolysis)

Microcirculation indicators

The data obtained by us showed significant differences in microcirculation rates between the intervention and comparison groups.

FAI decreased by 0.34 in the intervention group in men and by 0.35 in the control group. In women, FAI decreased by 0.42 in the intervention group, while in the control group it increased by 0.22 ($p< 0.001$) As for the ASI, it decreased by 2.61 in men in the intervention group and by 3.18 in women. In the control group, on the contrary, this indicator increases by 0.84 in men and by 0.56 in women ($p< 0.001$).

The BFI indicator differs significantly in the accommodation and comparison group. In the intervention group, the BFI decreased by 1.41 in men and by 1.94 in women ($p< 0.001$). In the control group, there was a slight increase in this indicator in both sex groups ($p< 0.001$).

Thus, after the course of disaggregant therapy, statistically significant positive shifts in the characteristics of the BFI were revealed. This concerned the decline in the indices of FAI, **ASI**, BFI. As for their individual components, the most distinct positive changes were in the characteristics of improved blood flow, decreased sludge, increased number of capillaries, and vasodilation. In the control group, where disaggregant therapy was not performed, there were some negative shifts in MC indicators in the form of deterioration of blood flow, increased sludge, and vasoconstriction.

MULTIVARIATE ANALYSIS OF RESEARCH RESULTS

A step-by-step logistic analysis of the relationship between the main risk factors and the prevalence of CHD independently and in conjunction with hemostasis and MC factors showed that when only the main risk factors were included in the model, the presence of DLP ($p< 0.001$), nationality ($p< 0.001$), and arterial hypertension ($p< 0.003$) have an independent relationship with the prevalence of CHD, and in women, DLP ($p< 0.0001$) and nationality ($p< 0.03$). In men, the relative risk between the first and fourth quartile of the generalized risk is 5.9.

and in women 3.6

The addition of hemostasis and fibrinolysis to the model significantly improves the differentiation of individuals with or without coronary artery disease. At the same time, such factors as nationality and DLP ($p< 0.001$) remain important in men, and FDPs ($p< 0.001$), fibrinogen ($p< 0.0001$) and ethanol test remain important in men.

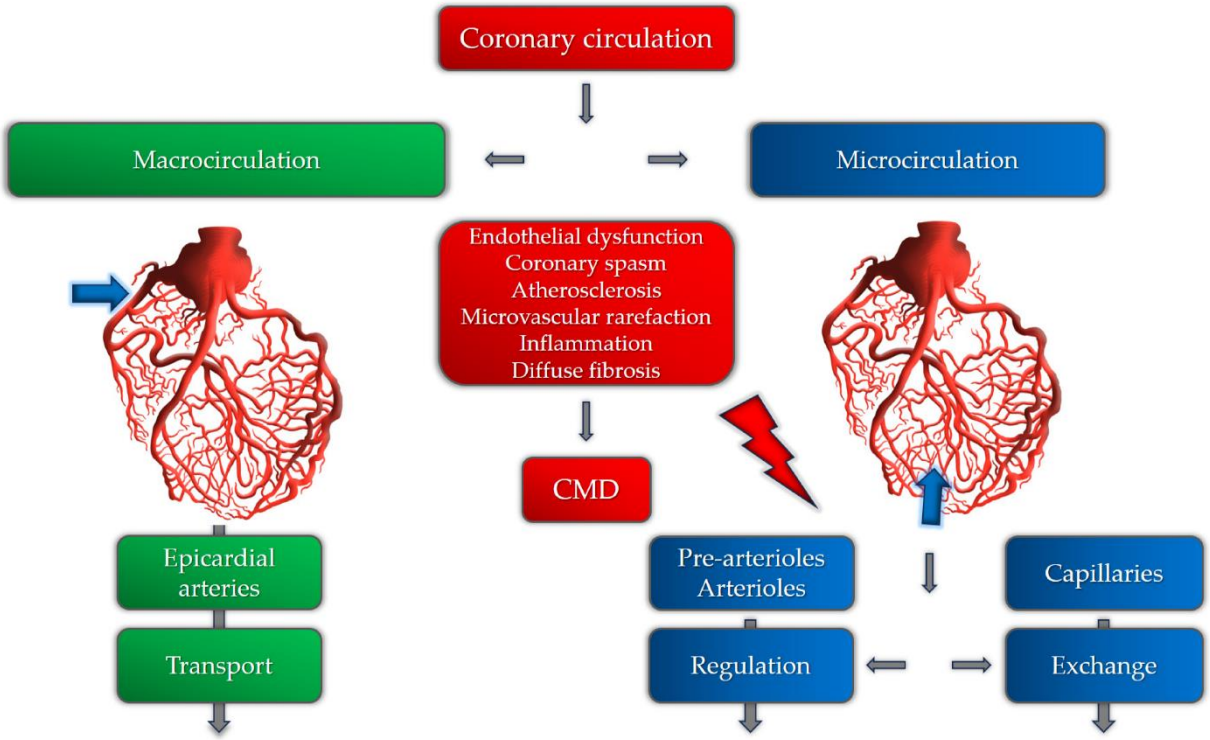
These parameters significantly improve the classification of the risk group, with the relative risk between the first and fourth quartile reaching 16.4. In women, after the introduction of hemostasis indicators into the model, nationality and DLP retain their high significance, and the

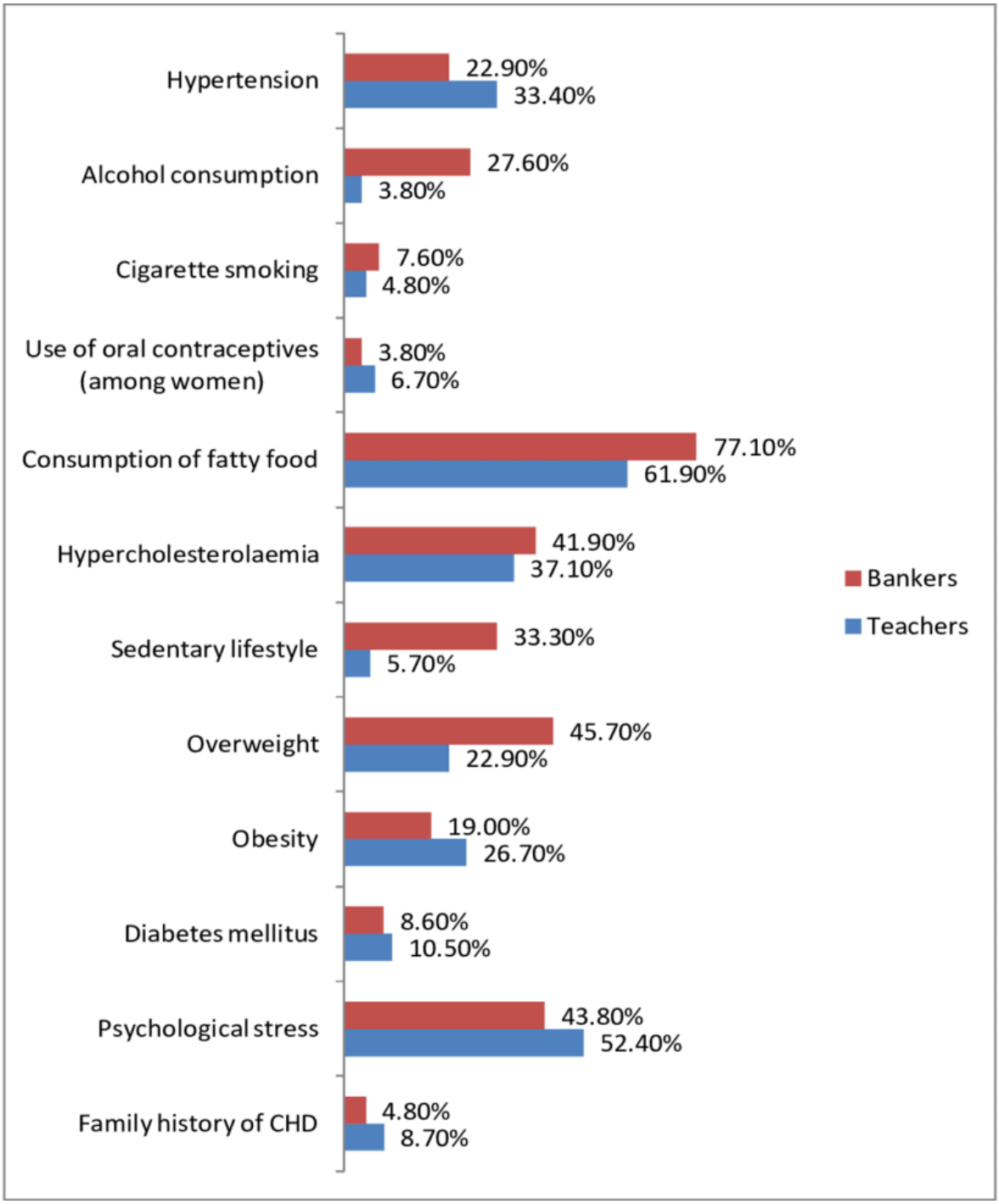
ethanol test (p< 0.0001) retains an independent contribution to the hemostasis indicators, while the relative risk increased by almost 1.7 times compared to the first model. And finally, the third model included, in addition to the main risk factors, microcirculation indicators. In this case, nationality and DLP remained important among the main factors for men. (p< 0.0001), but became a significant BMI (p< 0.01). Of the microcirculation indicators, SI (p< 0.0001) and ASI (p< 0.01) became significant. Taking into account these factors, the relative risk between the first and fourth quartile reached 37.1, which suggests that the inclusion of microcirculation indicators in the assessment of the presence of CHD significantly improves the differential diagnosis of CHD.

In women of the same model, only hypertension and DLP from the main factors and BFI from microcirculation indicators (p< 0.003) are significant. At the same time, the model shows a significant increase in the level of prediction to the level of relative risk to 14.7, although this turns out to be lower than in men by 2.5.

The total parameters in the systems of hemostasis, fibrinolysis and microcirculation in the multivariate analysis were more significant than the main risk factors, both among men and women.

When assessing the parameters of the microcirculation system, the leading ones that had an independent relationship with the prevalence of CHD were SI and BFI in the form of an aneurysm, both arterioles and venules, their tortuosity, capillary reduction, "sludge" syndrome of delayed and retrograde intermittent blood flow.




Hypertension
22.90%
33.40%
Alcohol consumption
27.60%
3.80%
Cigarette smoking
7.60%
4.80%
Use of oral contraceptives (among women)
3.80%
6.70%
Consumption of fatty food
77.10%
61.90%
Hypercholesterolaemia
41.90%
37.10%
Sedentary lifestyle
33.30%
5.70%
Overweight
45.70%
22.90%
Obesity
19.00%
26.70%
Diabetes mellitus
8.60%
10.50%
Psychological stress
43.80%
52.40%
Family history of CHD
4.80%
8.70%
Bankers
Teachers

Multivariate analysis made it possible to assess the independent contribution of both the main risk factors and the signs of microcirculation in the occurrence of new cases of coronary artery disease. Analysis of the association of the risk of developing new cases of CHD with the main risk factors using multiple logistic regression showed that in men, age and DLP contribute to its increase, and the relative risk of developing pathology in the fourth risk quartile increases by 6.2 times compared to the first. In women, only age remains significant in the model, and the relative risk increases 9.6-fold from the first to the fourth quartile (Figures 7.3 and 7.4). Perhaps this is because all other factors are very closely related to age and therefore do not make an independent contribution to the level of risk. The introduction of hemostasis and fibrinolysis indicators in men into this model makes age significant, and the time of thrombin formation, SF, and fibrinogen make a significant contribution to hemocoagulation indicators, while the relative risk of the disease increases to 14.2 times.

In women, in addition to age and hypertension, a significant contribution of soluble fibrin and fibrinogen is made, and the relative risk in this model increases to 29.0 times.

Therefore, it can be concluded that the introduction of such hemostasis indicators as soluble fibrin and thrombin formation time, fibrinogen into the model significantly improves the ability to predict the development of new cases of CHD in the population.

We specifically considered the additional contribution of microcirculation indicators in the prediction of new cases of coronary artery disease, for which we introduced FAI, ASI and BFI instead of hemostasis indicators into the model, while the predictive value of the model compared to the first two models (main factors and hemostasis) significantly increased in men. At the same time, the relative risk between the first and fourth quartiles was 17 times in men and 26 times in women. At the same time, the significant factors in men are BFI, FAI, and in third place is the DLP, and in women it increases accordingly. BFI and FAI. The leading elements of the intravascular index (ICI) were sludge syndrome, slow and retrograde blood flow, and intermittent blood flow.

Thus, when conducting a multifactorial analysis of generally accepted risk factors and studied specifically in this study in the form of an assessment of the hemostasis system, fibrinolysis and microcirculation system, it was revealed that the predictors of the course of IB among the main risk factors for our region are DLP, AH, BMI. Of the newly studied risk factors, the total characteristics of the hemostasis system, fibrinolysis with the detection of hypercoagulable shifts (thrombin time, fibrinogen, SF) and fibrinolysis depression (FDPs, ethanol test) are of significant prognostic significance. These indicators make an independent contribution to the development of CHD and can be attributed to predictors.

FAMILIAL RELATIONSHIPS OF HEMOSTASIS, FIBRINOLYSIS AND MICROCIRCULATION IN THE STUDIED POPULATION

To assess the genetic relationship between the levels of hemostasis and fibrinolysis in the populace, we conducted a family study in which we examined more than 80 siblings and proband spouses with hemocoagulation disorders with or without CHD.

Familial Relationships of Hemostasis Indicators

The obtained data showed that in comparison with the population, AT-III in probands was lower by 4.2 ($p<0.01$). At the same time, we have not found any significant differences between the probands and the siblings. The differences were only 0.4% (p"0.1). As for spouses, the differences were quite high and amounted to 7.7 ($p<0.05$).

The FDPs of probands were 1.7 higher than those of the population ($p<0.01$), while the FDPs of siblings were identical to those of probands ($p>0.1$), but significantly higher than in the population ($p<0.01$).

Soluble fibrin in probands was 1.6 mg/dL higher than in the general population ($p<0.001$), but the difference between its concentration and that of siblings was only 0.9 mg/dL higher ($p>0.1$). Free heparin in all the studied groups turned out to be indistinguishable from each other. Of interest is the close dependence of the ethanol sample in siblings **and** probands. In both groups, its values were significantly higher than in the population ($p<0.05$).-

Mean values of hemostasis indices in the population

	Population indicators of probands, siblings, spouses							
	M	**m**	**M**	**m**	**M**	**m**	**M**	**m**
AT-Sh	76,0	0,4	71,8	1,1	72,2	2,1	79,9	2,7
FDPs	12,1	0,3	13,8	0,7	14,1	2,2		
SF	6,8	0,2	8,4	0,4	7,6	0,4	6,4	0,3
St.**Heparin**	7,6	0,2	8,0	0,4	7,7	0,6	7,9	0,6
Ethanol sample	0,8	0,02	M	0,06	1.0	20,05	0,6	0,1
PTI	9,3	0,4	97,7	0,9	95,1	1,7	2,1	1,2
FG	5,2	0,1	6,6	0,3	6,3	0,4	4,8	1,4
FN	390,6	4,0	428,7	11,6	415,1	26,5	453,3	25,8

PTI in probands was 4.3% higher than in the general population ($p<0.001$). In siblings, the PTI level is between its values in the population and in the probands and did not differ statistically from either group. nor from the other group. The concentration of fibrinogen in the probands was *1.4* mg/dL higher than in the population ($p<0.05$). We have not established any differences between probands and siblings ($p>0.1$), while fibrinogen in siblings is much higher than in the population. With regard to fibronectin, it can be said that there is a tendency to

increase it in the group of probands and siblings, but due to the lack of observations, only the differences between the population and the probands are reliable.

Thus, when assessing hemostasis demonstrators in relation to family ties, it was found that the greatest dependence among probands and siblings is on AT-**III**, **FDPs**, ethanol tests, and fibrinogen. Of no particular interest to us is the established dependence between the proband and the sibling for AT-**III** in the form of its decrease, since there is information in the literature about the possibility of its congenital deficiency. A close relationship between probands and spouses has not been established.

Familial Connections of World Circulation Indicators

To study possible familial links between microcirculation indicators, we examined their levels among probands, **siblings**, and spouses.

Table 8.2 shows that the FAI of probands and siblings was the same (p>0.1), while that of spouses it was significantly lower (p<0.05). The ASI in probands and siblings does not differ significantly from each other (p> 0.1) and turns out to be significantly lower in spouses (p<0.05). Somewhat lower in spouses compared to probands and siblings turn out to be SIs, although these differences are not significant. At the same time, between siblings and probands, the SI level is almost identical (p>0.1)

The BFI of probands and siblings differs little from each other, although this indicator is higher among probands . However, it is much lower in spouses (p>0.01).

Table 8.2 Familial Relationships of Microcirculation Indicators

Indicators	Probands		Siblings		Spouses	
MC	M	m	M	m	M	m
FAI	1,2	0,06	1,1	0,11	0,6	0,15
ASI	13,0	3,6	14,3	1,2	9,6	1,3
SI	18,2	0,5	19,7	1,1	14,6	2,3
BFI	5,6	0,4	3,0	0,4	4,9	0,2

Thus, a comparison of microcirculation indicators in probands and relatives shows that all of them are significantly more important. Degrees have familial dependence, since almost all indicators are close to each other in siblings and wobands, and differ significantly in spouses.

The correlation analysis of the relationship between the main parameters of hemostasis and microcirculation between probands and siblings made it possible to establish a high correlation between the presence of CHD in the siblings selected by us (g-0.51, p<0.001). The CHD of siblings correlates with the BFI of probands (g"0.32, p<0.05) and, finally, to the greatest extent with the ztanol test (g-0.30, p<**0**,05). At the same time, there was no correlation between the prevalence of CHD in probands with spouses (p>0.5), although a high direct correlation was

found between the CHD of probands and spouses (g-0.42, p<0.01). The MUT of probands correlates with ASI (g-0.29, p<0.04) and SI (g<30, p0.05), and also correlates with the level of fibronectin (g=d, 35, p<0.02) (Table 3). 8.3.). A decrease in the latter is obviously a manifestation of the exhaustion of the body's protective reaction aimed at correcting the established disorders in the MC system.

Comparing the hemocoagulation indices in probands with the studied parameters of siblings and spouses, it can be noted that AT-III Probands is inversely correlated with the prevalence of hypertension in siblings (g "-0.38, p<0.01).

The most pronounced familial dependence of the highly significant of the hemostasis indicators of the ztanol test in probands with a number of other indicators of hemostasis in siblings (Table 8.4). The ztanol proband test is inversely correlated with the AT-III siblings:(g"-0.33, p<0.03) and directly with the level of soluble fibrin (g"-0.31, p<0.04) and the ethanol test of siblings (g=0.27, p<0.05).

Thus, it can be said that among the hemostasis indicators, the number of genetically determined indicators can be attributed to some extent the ethanol test, which has a family correlation with this feeder in siblings and with two other indicators of hemostasis. It is also characteristic here that between spouses with none of the

These indicators of a significant association were not found. In addition, it was found that the FAI of probands was associated with the ztanol test (g"0.32, p<0.04) and FDPs g "-0.1, p<0.04) in siblings. The ASI of probands is very highly correlated with the ASI (g-0.65, p<0.001), SI (g-0.60, p<0.001) and BFI (g" 0.55, p<0, 001) of siblings. An even higher correlation was found between the SI of probands with the **ASI** of siblings (r<0.67, p<0.001), SI (r0.65, p<0, 0001), as well as with the BFI (r=0.59, p0.001) of siblings.

Table 8. 3 Correlation matrix of the relationship between CHD and MC of probands with individual factors in siblings

Indicators	**IBS probands**		**Siberia**	
MC	**G**	**m**	**G**	**M**
CHD	0,46	0,01	0,06	0,68
ASI	0,25	0,08	0,29	0,05
SI	0,27	0,07	0,29	0,05
ISR	0,30	0,04	0,17	0,26
Ethanol				
sample	0,28	0,06	0,05	0,74
Fibronectin	0,16	0,32	0,35	0,02

The most pronounced familial dependence was found in the analysis of microcirculation indicators (Table 8.5). For example, the FAI of probands turns out to be closely related to the SII of siblings (r = 0.45, p<0.002), with the SI (r = 0.48, p <0.001), and finally with the BFI (r = 0)

As for the BFI of probands, it also turns out to be closely related to all indicators of microcirculation of siblings, so the correlation coefficient with the ARI is 0.55 (p<0.001), the relationship between BFI and SI is high (r = 0.50.r<0.0001) and with the BFI of siblings (r = 0.43, r<0.003).

Table 8.4 Correlation Matrix of Relationship of Proband Hemostasis Indices with Individual Factors in Siblings

Siblings	Proband					
	AT Sh		Reference assay		Fibronectin	
	R	M	r	m	R	m
AH	-0,38	0,01	0,18	0,30	0,13	0,40
LEI	-0,71	0,64	0,29	0,05	0,24	0,10
SI	-0,14	0,33	0,36	0,01	0,27	0,06
BFI	-0,21	0,15	0,42	0,01	0,18	0,23
AT-Sh	0,15	0,32	-0,32	0,03	-0,05	0,70
SF	-0,14	0,04	0,31	0,03	0,07	0,64
Reference assay	0,05	0,73	0,27	0,07	0,18	0,23

Table 8.5 Correlation matrix of proband microcirculation indices with individual factors in siblings

Siblings	Proband							
	IME		ISI		HIS		ИКР	
	r	m	r	M	r	m	R	m
CHD	0,23	0,12	0,38	0,01	0,36	0,01	0,30	0,04
ASI	0,45	0,00	0,65	0,00	'0,67	0,00	0,55	0,00
SI	0,48	0,00	0,59	0,00	0,64	0,00	0,50	0,00
BFI	0,50	0,00	0,55	0,00	0,59	0,00	0,43	0,01
AT-Sh	-0,26	0,00	-0,24	0,11	-0,30	0,05	-0,29	0,05
SF	0,28	0,08	0,31	0,04	0,34	0,02	0,31	0,04
PTI	0,29	0,07	0,35	0,03	0,40	0,01	0,39	0,01
Ethanol test	0,32	0,04	0,36	0,01	0,44	0,00	0,43	0,00
FDPs (IH)	0,31	0,04	0,32	0,33	0,42	0,00	0,44	0,00

It should also be noted that the ASI and SI of probands correlate with CHD in siblings (r=0.37.p<0.01 and d=0.3b, p<0.01), respectively.

Thus, correlation analysis does not allow us to deny, that changes in hemostasis and microcirculation in RVD cases are genetically determined, especially since the correlations of these indicators with the spouses of probands are insignificant and random.

In the course of a broader genealogical study, these questions may be more reliably established. However, the data obtained by us make it possible to use them in the development of a preventive direction in practical cardiology in order to improve the health of families burdened with coronary artery disease.

CONCLUSION

Cardiovascular diseases represent a major share of chronic cardiovascular disease and mortality in industrialized countries and are emerging as an important public health problem in developing countries. CHD is the most common cause of death in most countries around the world.

It should be noted that the incidence and mortality of CHD among young people has been increasing in recent years.

Over the past decades, the issue of the prevention and treatment of CHD has been addressed on a national scale, and experience has been gained in combating CHD and mortality from it through the implementation of numerous preventive measures. However, despite this, morbidity and mortality from CHD are still high. For many years, cardiovascular diseases have been in the first place in the structure of mortality of the working-age population.

All of the above makes the prevention of CHD and related problems in the form of the study of risk factors at the preclinical stage, the identification of more subtle risk factors, and the development of effective measures to reduce the incidence of the disease a primary task.

Data from epidemiological studies conducted both regionally and internationally have identified a number of factors that predispose to the development of coronary artery disease; gender, age, hypertension, smoking, high cholesterol, obesity, sedentary lifestyle, hyperuricemia, psycho-emotional stress, etc.

In recent years, thanks to the development of modern methodological approaches, the undoubted role of heredity in susceptibility to CHD has been shown.

Numerous clinical and experimental studies confirm the significant role in the pathogenesis of CHD disorders in the coagulation and anticoagulation systems, as well as autoimmune disorders in the development of both the disease itself and its main risk factors.

It is known that changes in MC, hemostasis, fibrinolysis, and blood rheology occur in parallel, occur in the early stages of CHD and progress as the severity increases. The emergence of methodological approaches to the study makes it possible to expand the understanding of changes in the vascular wall at the microcirculatory level and clarify their significance in the pathogenesis of coronary artery disease.

Population studies conducted in recent years in Central Asian regions, in particular in the Republic of Uzbekistan and the Fergana Valley, indicate an increase in the prevalence of CHD and its risk factors.

There are practically no population-based studies to study the role of the disorder in hemocoagulation systems, at the same time, it is impossible to obtain an objective assessment of the epidemiological situation with regard to CHD in the population without taking them into account.

This work is devoted to the study of one of the most urgent problems of population cardiology - prospective assessment of the main risk factors and relatively poorly studied in the poppularian genetic aspect in the form of disorders of the hemostasis system, fibrinolysis and microcirculation system in CHD in the unorganized population of the Republic of Uzbekistan in Andijan. These data make it possible to identify the preclinical stage of coronary artery disease.

To achieve this goal, the following tasks have been identified and solved:

The prevalence of CHD and the main risk factors in the population were studied. As new risk factors for coronary artery disease, the prevalence of indicators characterizing the systems of hemostasis, fibrinolysis and microcirculation in CHD has been studied.

The prevalence of CHD in connection with the above risk factors was studied.

A prospective study was conducted to identify new cases of CHD and deaths from CHD within 5 years, in this population, with the assessment of both the main, previously well-known and the above-mentioned poorly studied risk factors in the population aspect.

Changes in the system of hemostasis, fibrinolysis and microcirculation in a comparative aspect were studied in the intervention group during treatment with disaggregants and in the control group.

A multifactorial analysis of the study results was carried out. The family relationships of the indicators of the main risk factors and the systems of hemostasis, fibrinolysis and MC were clarified, and an epidemiological prospective study of the unorganized population of the city was carried out.

A random sample was organized from the latest electoral lists, which included all adults living in the survey area. Total indigenous and non-indigenous population (males and females 40-54 years old)

Andijan city was 15526 people.

From this array, a proportional 10% sample was formed by random numbers, which amounted to 1,553 people. 712 men and 462 women were examined. The coverage of the surveyed is 75.5%.

To identify CHD and its risk factors in the population and among proband family members, an epidemiological study, biochemical studies (TG, CH, alpha-cholesterol), studies of hemostasis and fibrinolysis system indicators were carried out:

A) Quantification of FDPs (biochemical and immunochemical method);

B) antithrombin level – 111 (TAt – 111)

C) the number of soluble fibrin monomer complexes (SF);

D) quantification of fibrinogen (FG);

E) Thrombin Formation Time (TT)

G) free heparin;

H) PTI – prothrombin index

i) benchmark test;

C) Fibronecthin (FN)

Biomicroscopy of the bulbar conjunctiva using a slit lamp (SL-56, 2B).

Statistical processing was carried out by means of the package of statistical programs SAS-82.4. The following were carried out: analysis of feature distributions and their numerical characteristics (mean, standard deviations, quartiles), analysis of simple relationships between variables (correlation analysis, contingency tables) in data subgroups, multivariate analysis of feature relationships and information features.

The organization of the database was carried out with the help of special software of the system for statistical analysis.

A multivariate analysis of the relationship between the prevalence of CHD and the main risk factors, lipid metabolism, hemostasis and fibrinolysis, and the state of the MC system was carried out using the logistic analysis procedure with a step-by-step selection of informative indicators at each step of selection, which makes it possible to judge the interdependence of indicators and the order of formation of the obtained models from other possible models. Based on the results of multivariate logistic analysis, risk functions were constructed to assess the risk of new cases of CHD depending on the value of the generalized SF, which is a linear combination of selected informative risk factors.

The analysis of the genetic material was reduced to the assessment of the correlation coefficient between the main factors of the claim and the disorder in the hemostasis system, MC (after adjusting for age). The distribution of indicators in relatives of probands with disorders in the system of hemostasis, fibrinolysis and MC was studied.

As a result of the study, the following factual data were established:

When studying the prevalence of CHD in the population of men and women aged 40-54, we found that certain CHD in men is more common than in women, as for the diagnosis of CHD according to extended criteria, they were higher in women. Significant differences have been reported between the prevalence of CHD in indigenous and non-indigenous populations of both

sexes. According to our data, definite CHD occurs in 12.7% of men (10.5% of indigenous and 17.2% of non-indigenous), and 20.8% of women (15.6% of indigenous and 30% of non-indigenous).

In men, there was an increase in the incidence of CHD with age in both ethnic groups, with the highest prevalence occurring among the non-indigenous population aged 50-54.

According to a number of authors, myocardial infarction was most often observed in men aged 40-49 years, while in women painless forms of CHD were registered with high frequency, especially at the age of 50-59 years.

In our studies, we explain a slight increase in the incidence of CHD by the negative impact of increasing risk factors and changes in people's lifestyle in our activities, i.e. by socio-psychological negative influences.

An increase in the incidence of CHD in industrialized countries is also associated with an increase in risk factors (HCH, HTG, hypoalpha-cholisterinemia, hypertension, obesity, smoking, etc.) and a change in lifestyle.

Among people with higher education, the number of cases of CHD in men was 2.4 times higher than in the group with less than secondary education, and a similar picture was observed in women. Our data on the prevalence of CHD in relation to the level of education coincide with the data of other researchers.

The prevalence of CHD is also influenced by the occupation of the respondents. In men, CHD is much more common among employees than among workers. However, the maximum number of CHDs was observed in the unemployed, which mainly includes pensioners, as well as those who do not work due to disability. These were older people and they had a more pronounced severity of coronary artery disease, since the disability was mainly determined by a disease of the cardiovascular system. In women, on the contrary, CHD is more common among workers than among employees.

DLP plays a significant role in the prevalence of CHD, since among individuals with dyslipoproteinemia, CHD occurred 1.9 times more often in men and 2 times more often in women, compared to individuals without DLP. The characteristics of lipid metabolism in men and women, taking into account age, sex of indigenous and non-indigenous composition, show that cholesterol was most elevated in indigenous males aged 45-49 years, and in non-indigenous people aged 50-54 years. Major hypercholesterolemia occurred in non-indigenous women aged 45-49 years.

The greatest reduction in alpha-cholesterol was among non-indigenous men aged 40-44 years and among non-indigenous women aged 40-44 years.

A comparison of the prevalence of HCH among the population shows that in Tashkent it was 21.3%, as well as 22.4%, respectively, among the indigenous and non-indigenous population. The prevalence of CHD increases with an increase in CH, TG and a decrease in alpha-cholesterol.

The population we studied was characterized by a high prevalence of hypertension. In men, hypertension was more common than in indigenous women, and in non-indigenous women, on the contrary.

Data on the prevalence of overweight show that men in all age groups have a lower number of people with a BMI than women. It should be noted that in young women of non-indigenous nationality, BMI is registered in 44% of the surveyed, which indicates insufficient propaganda of the harm of obesity.

It is characteristic that the number of smokers decreases with age among the indigenous population, while among the non-indigenous population, the proportion of smokers aged 40-44 and 50-54 is the same. There were no registered smokers among indigenous women, while among non-indigenous women, the proportion of smokers was 12.0 per cent, and more often in the youngest age group, which is generally typical for the population of many regions. A comparison of the data on smoking prevalence among the population obtained in Andijan shows that at an older age, the frequency of smoking and BMI decreases with age, which coincides with our data.

In the studied population, 53.6% of men and 13.2% of women drink alcohol. With age, the number of people who consume alcohol decreases. It is also characteristic of our population that in all age groups, indigenous men consume alcohol less often than non-indigenous men. Indigenous women accounted for 13 per cent of the population and only at younger ages, while non-indigenous women accounted for 35.8 per cent of drinkers. These peculiarities are obviously explained by religious relations, since according to Muslim laws the consumption of alcoholic beverages is generally prohibited, especially in the present period, when religion is developing without hindrance.

The age peculiarity of our region in connection with smoking and alcohol consumption is apparently associated with the understanding of the harm of these habits at a more mature age and to a certain extent is due to the growing influence of religion with age, which is prohibited, both smoking and drinking alcoholic beverages.

The following factors are the most generally accepted in clinical practice and the most informative in the assessment of the hemostasis system, fibrinolysis: PTI, fibrinogen, SF, ethanol test, which make it possible to judge the blood coagulation system and its readiness for

intravascular coagulation; while free heparin, AT-111, FDPs, fibronectin allow to assess the protective anticoagulation readiness of the body. These indicators were used to assess the state of the hemostasis and fibrinolysis systems in the studied population of men and women aged 40-54 years in Andijan.

The results of our studies show that PTI in men and women is not subject to age-related changes. The time of thrombin formation in the younger groups varies significantly, while in the older group of men it decreases from 20.5 to 16.10 seconds. This is indicative of increased thrombin formation. In men and women, the timing of thrombin formation does not differ significantly.

Fibrinogen rises slightly with age, in both men and women. The study of the content of soluble fibrin in age and sex groups revealed that its concentration increases with age in men and practically does not change in women. The level of SF at the age of 50-54 years increases by 2.7 mg/dL compared to the group of 45-49 years.

In all age groups, there was a decrease in free heparin in men, the lowest rates were at the age of 40-49 years. Mean levels of free heparin time were 1.3 seconds higher in women than in men.

A decrease in the level of antithrombin 111 with age (from 77.3 to 73.3 at the age of 50-54 years) is characteristic. The difference in AT-111 levels between men and women was 4.7%.
The study of FDPs by the biochemical method, as a factor used in the assessment of the protective anticoagulation readiness of the body, shows that FDPs tends to increase in men with age, in women in all age groups no significant difference was revealed. Overall, FDPs was slightly higher in women than in men, with the exception of the 50-54 age group, where they were almost identical. When determining FDPs by immunochemical method, similar data to the above and no age differences were established in both men and women.

We found no change in fibronectin in all ages and in both sex groups.

For the purpose of a more in-depth study of the relationship between hemostasis indicators and the prevalence of CHD in the studied cohorts, we determined the cut-off points of the distribution series, for which we divided the indicators into quartiles, taking into account the normal values of the given methodological recommendations.

The comparison shows that FDPs was within the normal range in 50% of the results obtained, At-111 in more than half of the examined was below normal, normal SF was found only in 25%, normal thrombin time was in 50%, and PTI in 75%, fibrinogen was increased in 25%. In the compared characteristics of FDPs and SF in our studies, an imbalance in the form of increased fibrin formation (SF) and inadequately small fibrin destruction (FDPs) was revealed.

The analysis of the data obtained made it possible to attribute the ratio of RF and FDPs towards an increase to a factor of high risk of coronary artery disease.

A comparative assessment of the relationship between each of the hemostasiological parameters and the prevalence of CHD was carried out and the boundaries of groups with different levels of risk of CHD development were determined.

Measuring the relationship between the prevalence of CHD and the level of AT-111 allowed us to conclude that with an increase in its level, the number of CHD cases in the population of both men and women decreases. With a low level of AT-111, CHD occurs 7.2 times – 2 times, respectively, more often than with a high one.

An analysis of the relationship between an inadequate small increase in FDPs content in comparison with the level of SF elevation and the prevalence of CHD showed that the number of CHD cases is increasing in men and women. Inadequate FDPs content in comparison with SF in patients is a sign of a relative increase in depression of fibrinolysis, a confirmation of an increase in hypercoagulating activity in the studied group of patients.

Studies of the relationship between the prevalence of CHD and the time of thrombin formation indicate that the lower this time, the higher the number of CHD cases.

According to our data, with a decrease in the concentration of free heparin, a linear increase in the incidence of CHD was observed.

In our research, we have found that PTI is also significantly correlated with the prevalence of CHD. Low PTI values coincide with a decrease in the number of CHD cases.

With an increase in the level of ethanol test, the incidence of CHD in men increased by 7.3 times, and in women by 4.9 times. Moreover, at any values of the ethanol test, the incidence of CHD in women is higher than in men.

According to our data, the differences in the prevalence of CHD at different levels of fibrinogen are also very indicative. As its level increases, the number of CHD cases increases from the first to the fourth quartile in men and women. It seems to us that the absence of a significant increase in fibrinogen content is due to the increase in latent coagulopathy of consumption, especially since this coincides with a similar dynamics of FDPs.

Comparison of the data obtained by us with the data of the literature shows that, according to some authors, signs of hypercoagulability were also found in the preclinical stage of coronary artery disease. The possibility of latent compensated DIC with increasing anticoagulation activity, but with signs of inhibition of enzymatic fibrinolysis, is indicated. The presence of major risk factors (AC, **HCH**, BMI, genetic burden, smoking) exacerbated disorders in the blood coagulation system.

For the final assessment of the causal relationship between the studied risk factors and the occurrence of new cases of CHD, a prospective follow-up was carried out 5 years after the initial c4screening of cohorts with known levels of risk factors without clinically pronounced pathology at the beginning of the study. Men and women were re-examined in full and new cases of CHD were detected.

In order to determine the prognostic significance of the indicators of the hemostasis and fibrinolysis system, a prospective assessment of the following hemostasiological indicators was carried out. It was revealed that in the absence of a decrease in the level of AT-111, the number of new cases of CHD does not increase, both in men and women

When analyzing the relationship between FDPs and the occurrence of new cases of coronary artery disease, we assessed this parameter in relation to the content of SF and fibrinogen. As mentioned above, the Russian Federation has a clear tendency to increase from the first to the fourth quartile. When comparing the FDPs and SF values, it turned out that the apparent increase in the FDPs content does not go beyond the norm in most cases. The content of SF statistically significantly increased, which is a reflection of the imbalance in the characteristics of these indicators for the presence of increased fibrin formation with inadequately low fibrin destruction.

The data obtained by us in a prospective study allow us to recommend an assessment of the ratio of SF and FDPs as a prognostic feature with a noticeable predominance of the former.
Analysis of thrombin formation by thrombin time in men showed that an increasing increase in thrombin formation, manifested by a shortening of thrombin time, corresponds. the emergence of new cases of CHD, which clearly increases from the first to the fourth quartile, where the number of new cases of CHD was 12 times higher than in the first. In women, a similar but weaker pattern was observed.

When comparing these data with the picture obtained when studying the prevalence of CHD in men and women, we found that the relationship curves are identical, which made it possible to consider this indicator as a prognostic factor.

Comparison of the relationship between the value of free heparin and CHD showed an increase in the number of new cases of CHD with a decrease in this indicator. The established relationship between this indicator and the prevalence of CHD makes it possible to recommend this indicator among the prognostically significant factors of CHD progression. Our data show that with the increase in the content of PTI, there is an increase in new cases of CHD in both men and women. In both sexes, an increase in the value of the ethanol test and an increase in new cases of CHD were revealed.

Of particular interest is the analysis between the content of fibrinogen and the occurrence of new cases of coronary artery disease. It was revealed that with an increase in the content of fibrinogen, there is an increase in new cases of coronary artery disease. At the same time, the maximum number of cases falls on the third and fourth quartile in men and women. In our opinion, the absence of a clear increase in fibrinogen content may be associated with an increase in the clinical severity of CHD and the occurrence of coagulopathy of consumption with the transition of fibrinogen to fibrin. Moreover, these individuals have an increased content of SF and a tendency to the absence of a significant increase in FDPs.

Based on the above data, an increase in fibrinogen content in patients with progressive CHD is a highly informative, prognostically unfavorable sign. However, a comprehensive assessment of fibrinogen, FDPs and SF, taking into account the clinical picture of the disease, seems to be the most valuable and significant. The latter will make it possible to ascertain not only the signs of hypercoagulability, but also the transition of the quantitative increase of the latter into a qualitative state (DIC syndrome – transition of FG to fibrin).

Dynamic assessment of the content of fibronectin showed that it tends to increase in parallel with the emergence of new cases of coronary artery disease.

Thus, in the univariate analysis, the clearest dependencies between the occurrence of new cases of CHD and the indicators of hemostasis, fibrinolysis were registered in relation to thrombin time, fibrinogen, AT-111 and the ratio between SF and FDPs, which is a condition for increasing the blood coagulation capacity in the form of accelerated thrombin-, fibrin formation with a decrease in the activity of the anticoagulation system (inhibitor of coagulation AT-111 and depression of fibrinolysis).

The study of MC indicators in the population has shown that they are all subject to age-sexual changes. FAI in males increases with age in both indigenous and non-indigenous populations. There are no age-related ethnic differences among women. FAI increases with age in indigenous men, while there are no age differences in non-indigenous men. A similar pattern is observed in women, but no increase is observed in the non-indigenous population. Analysis of the relationship between the indicators of microcirculation systems and the prevalence of CHD indicates its high informative value. Thus, with an increase in the total index, there is a significant increase in the number of CHD cases, both in men and women.

There is also a clear link between individual representatives of the S&I. Thus, the difference between the first and fourth quartiles and SI was 12.7 times in men and 5.1 times in women. At the same time, it was revealed that the most important elements of ASI influencing the prevalence of CHD were the following: a significant decrease in the number of arterioles, capillaries,

narrowing of arterioles. Pronounced irregularity of their lumen, aneurysmal changes in them, multiple spindle-shaped aneurysms of venules, an increase in their tortuosity, as well as a pronounced narrowing of arteriole precapillaries, dilation of venous postcapillaries in the limbus. An equally pronounced association between BFI and the prevalence of CHD was found. The leading elements of the blood flow index most closely related to the prevalence of CHD were the following: delayed and retrograde blood flow, and the "sludge" syndrome) of FAI the most significant were lipid deposition and haemosiderosis.

In the analysis of the detected changes in the BFI, it follows that the strongest element of the ASI is the emptying of the capillaries (reduction from the number of the visual field). Other elements were in a direct, close relationship with this indicator with high statistical significance. From the characteristics of BFI in connection with the prevalence of CHD, it follows that there is a pronounced disorder both in the characteristics of the vascular wall and blood flow, as well as perivascular changes that are highly correlated with the prevalence of CHD. Our data are supported by the literature that microcirculation disorders in atherosclerosis are systemic and directly related to the severity of the disease.

Thus, the generally accepted opinion that atherosclerosis of large vessels is the basis of coronary artery disease can be supplemented by the presence of an organic lesion of the BFI, which is responsible for the implementation of transcapillary exchange.

Subsequently, an analysis of the relationship between the indicators of the BFI system and the occurrence of new cases of CHD, identified during prospective observation, was carried out. SI is closely associated with the emergence of new cases of coronary artery disease. As SI levels rise, so does the number of new CHD cases. In the fourth quartile, it is 10 times for men, 4.7 times for women (compared to the first quartile).

Also, the increase in ASI is accompanied by an increase in the number of new cases of CHD in both men and women.

We observed a clear relationship between the occurrence of new cases of CHD and the magnitude of BFI. In the fourth quartile, the number of new cases in women is 14 times higher than in the first, and in men 11.8 times. FAI is relatively weakly associated with the occurrence of new cases of coronary artery disease.

From the above data, it follows that all the MC indicators we selected can be used as a prognostic index, however, the clearest relationship can be traced between the number of new cases and BFI, which can be recommended as the leading indicator of MC responsible for the progression of CHD. It should be attributed to the predictors of the course of coronary artery

disease, which can be used in combination to diagnose the preclinical stage of the disease during preventive studies.

Of considerable interest is the study of the combined effect of the prevalence of coronary artery disease, the main risk factors and previously little-known indicators of the MC system.
Studies have shown that attaching the pathological value of ASI to any set of risk factors significantly increases the prevalence of coronary artery disease. For example, the combination of DLP with increased ARI increased the prevalence of CHD by 2.4 times. A similar pattern is observed for various combinations of ASI with other risk factors.

The combination of BFI with other risk factors also significantly increases the prevalence of CHD. In this case, where BFI is the only factor, CHD is more common than in individuals without any of them. When this factor is combined with others, CHD is even more common, especially when an elevated BFI is combined with DLP and BMI.

The high value of ASI, in combination with other societal factors, leads to a significant increase in the number of CHD cases, which is especially pronounced when combined with DLP and BMI, where the prevalence of CHD in the studied population significantly increases.
Thus, the material convincingly indicates the importance of disorders in the MC system as an important risk factor for CHD and allows to significantly improve diagnostics in the preclinical and clinical stages, to choose the most optimal approaches to both primary and secondary prevention of this pathology.

The revealed abnormalities in the systems of hemostasis, fibrinolysis, and MC in patients with CHD put forward the need for preventive and therapeutic intervention.

People in the intervention group received disaggregation therapy in the form of aspirin 0.25 times a day for 2 months. The comparison group (control) did not receive treatment with disaggregants.

A dynamic study of lipid metabolism (cholesterol, alpha-cholesterol, triglycerides) did not reveal a significant difference in any of these parameters in the compared control and intervention groups.

Analysis of the data obtained during the study of the hemostasis and fibrinolysis systems showed that all indicators undergo significant changes under the influence of disaggregation therapy.

Antithrombin-111 increased in both men and women in the intervention group, while levels did not change significantly in the control group. SF and FDPs decreased in the intervention group and there was a slight increase in the control group.

The study of thrombin formation time shows that it was prolonged in the intervention group, and in the control group there was a slight shortening of thrombin. This applies to both men and women. It should be noted that there is an inversely proportional relationship between the time of thrombin formation and thrombinogenesis, i.e. the data obtained indicate a decrease in thrombinogenesis in the intervention group.

A similar pattern was found for free heparin time. In the intervention group, the prothrombin index decreased in both sexes, while in the control group there was no significant positive dynamics.

As for fibrinogen, fibrinogen levels in both men and women decrease, although not to the same extent, and do not change significantly in the control group. There was no statistically significant difference in fibronectin characteristics in both the intervention group and the control group.

Thus, under the influence of the prophylactic treatment, the indicators of FDPs (determined by biochemical and immunochemical methods) of SF, PTI, and fibrinogen decreased. It should be noted that at the same time, the content of AT-111 increased, the time of thrombin formation and free heparin was lengthened. In the control group, there were no positive changes in the hemostasis index with some deterioration in a number of them.

Thus, on the basis of the data obtained, we conclude that the therapy with disaggregants had a positive effect in both men and women with disorders in the hemostasis systems. The latter consists in a statistically significant limitation of latent increased thrombin and fibrin formation (DIC) due to a decrease in both plasma procoagulant activity and due to the activation of coagulation inhibitors (AT-111, heparin).

Our data on changes in the microcirculation system after disaggregated exposure showed that they had a significant difference in the compared groups. In this analysis, we considered the changes in FAI, ISI, BFI.

Positive dynamics was obtained in the indices of ISI, FAI, BFI in the form of a significant decrease in the "sludge" syndrome, an increase in the number of active capillaries, and a decrease in the toning of the arterial precapillary after disaggregant therapy in the intervention group. In the control group, some negative changes were noted in the form of deterioration of microcirculation indicators.

A step-by-step logistic analysis of the main risk factors with the prevalence of CHD independently and in conjunction with hemostasis and MC factors showed that when only the main risk factors were included in the model, the presence of DLP, nationality and hypertension had an independent relationship with the prevalence of CHD, and in women DLP and nationality.

In men, the relative risk between the first and fourth quartile of the generalized risk is 5.9, and in women 3.6.

Adding hemostasis and fibrinolysis to the model dramatically improves the differentiation of individuals with and without coronary artery disease. At the same time, such factors as nationality and DLP remain important in men, and FDPs, fibrinogen and ethanol test from hemostasis indicators.

These parameters significantly improve the classification of the group, with the relative risk between the first and fourth quartile reaching 13.4. In women, after introduction into the model, the indicators of hemostasis, nationality and DLP remain high, and the independent contribution of the hemostasis indicators remains

Ethanol test, with the relative risk increased by almost 1.7 times compared to the first model.

And, finally, the third model included, in addition to the main risk factors, MC indicators. In this case, in men, nationality and DLP remained the main factor, but BMI became one of the most important factors. Of the MC indicators, SI and ASI became significant. Taking into account these factors, the relative risk between the first and fourth quartile reached 37.1, which suggests that the inclusion of MC indicators in the assessment of the presence of CHD significantly improves the differential diagnosis of CHD.

In women in the same model, only hypertension and DLP from the main factors and BFI from the MC indicators are significant. At the same time, the model shows a significant increase in the level of prediction to the level of relative risk of 14.7, although this turns out to be 2.5 times lower than in men.

In the assessment of the indicators of the MC system, the leading ones that had an independent relationship with the prevalence of CHD were SI and BFI in the form of aneurysm, both arterioles and venules, their tortuosity, capillary reduction, sludge syndrome, delayed and retrograde intermittent blood flow.

Multivariate analysis allows us to assess the independent contribution of both the main risk factors and the signs of the occurrence of new CHD cases that we are studying. Analysis of the association of the risk of developing new cases of coronary artery disease. Analysis of the association of the risk of developing new cases of CHD with the main risk factors using multiple logistic regression showed that in men, age and DLP contribute to its increase, and the relative risk of developing pathology in the fourth risk quartile increases by 6.2 times compared to the first. In women, only age remains significant in the model, and the relative risk from the first to the fourth quartile increases by a factor of 9.6.

The introduction of hemostasis and fibrinolysis indicators in men into this model makes age significant, and of the hemocoagulation indicators, a significant contribution is made by TT, SF, FG, while the relative risk of the disease increases to 14.2 times.

In women, in addition to age and hypertension, the level of soluble fibrin and fibrinogen makes a significant contribution, and the relative risk in this model increases to 29.0.

Therefore, it can be concluded that the introduction of such indicators as hemostasis, SF and time of thrombin formation, FG into the model significantly improves the ability to predict the development of new cases of CHD in the population.

We specifically considered the additional contribution of MC indicators in the prediction of new cases of coronary artery disease, for which we introduced into the model instead of hemostasis, AII, ASI and BFI indicators, while the predictive value of the model compared to the first two models (main factors and hemostasis) significantly increased in men, while the relative risk between the first and fourth quartiles was 17 times in men. and in women, it reaches 26. At the same time, the significant factors in men are BFI, FAI, and in third place is DLP, and in women, age, BFI and FAI, respectively. The leading elements of the intravascular index (ICI) were sludge syndrome, slow and retrograde blood flow, and intermittent blood flow.

Thus, when conducting a multifactorial analysis of generally accepted risk factors, and studied specifically in this study in the form of an assessment of the hemostasis system, fibrinolysis and the MC system, it was revealed that the predictors of the course of CHD among the main risk factors for our region are DLP, AH, BMI. Of the newly studied risk factors, the total characteristics of the hemostasis system, fibrinolysis with the detection of hypercoagulable shifts (TT, FG, SF) and fibrinolysis depression (FDPs, ethanol test) are presented. These indicators make an independent contribution to the development of CHD and can be attributed to its predictors.

To assess the genetic relationship between the levels of hemostasis and fibrinolysis in the population, we conducted a family study in which siblings and proband spouses with hemocoagulation disorders with or without CHD were examined.

The results of the study showed that compared to the population, the number of AT-111 in the probands was lower. The level of AT-111 was found to be low in probands and siblings. The differences were only 0.4%, as for spouses (husbands and wives of probands), the differences were quite high and amounted to 7.7.

FDPs s in probands were higher than in the population. As for free heparin, it turned out to be indistinguishable from each other in all the studied groups.

Of considerable interest was the close dependence of the ethanol sample in siblings and probands. In both groups, its value was significantly higher than in the population.

PTI in probands turned out to be significantly higher than in the population. In siblings, the PTI level was between its values in the population and in probands. The concentration of fibrinogen in probands and siblings was greater than in the population. There is no distinction between probands and siblings.

Thus, when assessing hemostasis indicators in relation to family ties, it was found that the greatest dependence among probands and siblings is on AT-111, FDPs, ethanol test, and fibrinogen.

We have not found a close correlation in the spread of the above-mentioned hemostasiological parameters between probands and spouses.

A study of the familial relationship between microcirculation indicators showed that the FAI in probands and siblings turned out to be the same, while in spouses they turned out to be lower.

The ASI also in probands and siblings does not differ significantly from each other and turns out to be much lower in spouses.

In comparison with probands and siblings, the SI is slightly lower in spouses, and its level is almost identical between siblings and probands.

The BFI of the probands turned out to be slightly lower than that of the siblings. The results obtained by comparing the indicators of microcirculation in probands and relatives make it possible to conclude that all of them have a significant family dependence, and almost all these indicators are close to each other in siblings and probands and differ significantly in spouses.

The correlation analysis of the relationship between the main parameters of hemostasis and microcirculation in probands and siblings allowed us to establish a high correlation between the presence of CHD in siblings and probands selected by us. At the same time, it was revealed that CHD correlates with the BFI of probands. There is no correlation between probands and spouses in this regard, although a direct correlation has been established between the CHD of probands and the FAI of spouses. It seems to us that the latter may be due to the environmental factor in the form of the same nutrition in the family.

Comparison of hemostasiological parameters in probands with the studied parameters of siblings and spouses showed that AT-111 of probands is inversely correlated with the prevalence of hypertension in siblings.

The most pronounced dependence was found in the characteristics of the ethanol sample in probands with a number of other indicators, since it is inversely correlated with the AT-111 of siblings and directly with the SF level.

Thus, it can be concluded that the ethanol test can be attributed to the number of genetically determined indicators to a certain extent. It is also characteristic that no significant relationship was found between the spouses with any of these indicators.

In our studies, the most pronounced familial dependence was found in the analysis of microcirculation indicators. For example, the FAI of probands turns out to be closely related to the SI (Total Index), and the SIBs of siblings with the Total Index, with the BFI. Also, the FAI of probands is associated with ethanol assay and FDPs in siblings. An even greater correlation was established between the SI of the probands with the SII of the siblings, the SI, as well as the BFI of the siblings.

The BFI of the probands turns out to be closely related to the microcirculation indices of the ISI, BFI, SI and BFI of the siblings.

It is also noteworthy that the indicators of microcirculation of probands are closely related to a number of hemostasiological parameters of siblings. The ethanol assay is related to the FAI, ISI, SI and BFI of the probands.

The correlation analysis does not exclude that changes in hemostasis and microcirculation in a number of cases are genetically determined. The data obtained by us make it possible to use them in the development of a preventive direction in practical cardiology in order to improve the health of families burdened with coronary artery disease.

Thus, a study conducted at the population and family level in the Fergana Valley of the Republic of Uzbekistan confirmed the importance of generally accepted main risk factors and revealed an independent contribution of disorders in the systems of hemostasis, fibrinolysis and microcirculation in the occurrence and development of CHD.

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