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Учреждение образования  
«Гомельский государственный медицинский университет»

Кафедра патологической физиологии  
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Протокол №7 от 30.08.2017

**МЕТОДИЧЕСКАЯ РАЗРАБОТКА**  
Для проведения занятия со студентами  
3 курса ФПСЗС, обучающихся на английском языке  
по патологической физиологии

Тема: **Патология системы гемостаза**

Theme: **Pathology of hemostasis system**

Время 3 ак. часа

**1.Actuality of the theme.** The liquid state of blood is provided with difficult interaction of three systems – coagulative, anticoagulative and fibrinolytic. Alteration each of them can cause to decrease or increase of coagulation of blood. The decrease of coagulation(hypocoagulation) appears like hemorrhagic syndrome. It's appears as results of alteration thrombocytous-vessels hemostatic(thrombocytopenia and thrombocytopathia) or disturbance of various stages of coagulation of blood (hemophilia A, B, C, afibrinogenemia). The increase of coagulation of blood (hypercoagulation) is considered as major mechanism formation of thrombus. One of the most serious consequences alteration of hemostasis, which includes both hyper- and hypocoagulation, is syndrome of disseminated intravascular coagulation of blood – DIC-syndrome. It develops as complication in traumatic, anaphilaxic or cardiogenic shock, malignant tumours, acute kidney insufficiency, exfoliation of placenta, septicemia, massive hemolysis. The consequences of disturbances coagulation of blood quite often acquire menacing character and demand emergency measures from the medical staff.

**Learning goals of the lesson:** to study etiology, pathogenesis and clinical manifestations of hemostasis system disorders.

**Educational goals of the lesson:** formation of scientific outlook and theoretical basis of future specialists on the basis of fundamental knowledge and the latest achievements of pathological physiology.

**Objectives of the lesson:**

1. To know etiology and pathogenesis of platelet-vascular hemostasis in thrombocytopenia, thrombocytosis, thrombocytopathy;
2. To know causes and mechanisms of disorders of coagulation hemostasis;
3. To know principles of classification, etiology and pathogenesis of DIC syndrome.
4. To know hemorrhagic and thrombotic syndromes

**To repeat the following questions from related disciplines to ensure absolute mastery of the material:**

1. Scheme of thrombopoiesis (histology, cytology, embryology disciplines).
2. Methods of determination of thrombocyte count, coagulogram (normal physiology discipline).

**Control questions of the lesson:**

1. Mechanisms of hemostasis. Primary and secondary physiological anticoagulants.
2. Pathology of vascular-platelet hemostasis: types, causes, mechanisms of development, manifestations.
3. Pathology of coagulation hemostasis: types, etiology, pathogenesis, manifestations.
4. Syndrome of disseminated intravascular coagulation (DIC-syndrome): etiology, principles of classification.
5. Pathogenesis, main clinical manifestations and principles of diagnosis of DIC syndrome.
6. Vasopathy.
7. Principles of correction of hemostasis disorders.

**Calculation of study time**

Total study time 3 ac.hours

№ п/п	Contents	Calculation of study time
1.	Introduction. Motivational characteristic of the theme	3 minutes
2.	Written control of students on the topic of the lesson	15 minutes
3.	Interviews with students about the topic of the lesson	60 minutes
4.	Self-managed student work	15 minutes
5.	Summing up the results of the lesson	5 minutes
6.	Decision of situational tasks	20 minutes
7.	Task for the next lesson	2 minutes

### Additional material:

Hemostasis system – is a combination of biological and biochemical mechanisms that maintain liquid circulating blood, maintaining the integrity of blood vessels and arresting bleeding when they are damaged.

Microcirculation in organs and tissues and level of their blood supply to a large extent depends on the functioning of the hemostatic system. The pathology of this system is manifested by bleeding, development of thrombosis, infarcts and ischemia of organs. Hemostasis is carried out by three interacting with each other morphological and functional components: the walls of blood vessels, blood cells (primarily platelets) and plasma systems - coagulation, anticoagulation, fibrinolytic (plasmin) and kallikrein-kinin.

Blood vessels and platelets the first react to injury (primary hemostasis), followed by blood coagulation occurs with the participation of plasma factors (secondary), although both of these mechanisms are mutually potentiate each other and function conjugately.

### THROMBOCYTOPOIESIS

First morphologically recognizable cell of this series is megakaryoblasts. Further development of the cells is carried out by endomitotic way, occurs repeatedly doubling the number of chromosomes without cell division. Formed promegakaryocyte, then megakaryocyte – representing the polyploid cells with the number of nuclei, reaching 128 (the main part of megakaryocytes contain 8-16 nuclei). The process of converting megakaryoblasts in megakaryocytes lasts about 25 hours. The life cycle of megakaryocytes is about 10 days. Platelet production is carried out by the bud off cytoplasm from the megakaryocytes.

### COAGULATIVE AND ANTICOAGULATIVE SYSTEMS

#### Platelet clotting factors

Factor 1 – platelet accelerator globulin identical factor V,

Factor 2 – accelerator thrombin, fibrin plastic factor (accelerates the conversion of fibrinogen),

Factor 3 – platelet thromboplastin, partial thromboplastin,

Factor 4 – anti-heparin factor,

Factor 5 - clotting factors (immunologically identical to fibrinogen),

Factor 6 – trombostenin,

Factor 7 – platelet co-thromboplastin,

Factor 8 - anti fibrinolysin,

Factor 9 - fibrin-stabilizing factor, by the action corresponds to factor XIII,

Factor 10 - 5-hydroxytryptamine, serotonin,

Factor 11 - adenosine diphosphate (ADP).

Table 19. Plasma coagulation factors

Number, trivial name	Function	Place of formation	Activation factors and mechanism of action
<b>I fibrinogen</b>	Structural protein	Hepatocytes	Converted by thrombin to fibrin (Ia - basic substance of thrombus). Participates in platelet aggregation. Promotes tissue repair
<b>II prothrombin</b>	Zymogen of serine protease of thrombin	Hepatocytes	Under the influence of active prothrombinase converted into thrombin (IIa). Activates fibrinogen to form fibrin
<b>III Tissue thromboplastin or apoprotein III</b>	Transmembrane protein	Endothelial cells, macrophages Released at injury of the vessel wall, tissues	Cofactor of factor VII, triggers the extrinsic pathway of blood coagulation

Number, trivial name	Function	Place of formation	Activation factors and mechanism of action
<b>IV</b> calcium ions – $\text{Ca}^{2+}$		Platelet granules (dense bodies), absorbed from the intestine	Participates in the formation of complexes of plasma factors and lipids. Is part of the active prothrombinase. Promotes platelet aggregation. Bind heparin. Participates in the formation of the primary hemostatic plug and thrombus retraction. Inhibits fibrinolysis
<b>V</b> Proaccelerin, labile factor, accelerator (Ac-) globulin	Protein cofactor	Hepatocytes, megakaryocyte, platelet	Activated by factor IIa. Is part of the active prothrombinase. Creates optimal conditions for the interaction of factor Xa and II
<b>VII</b> Proconvertin, serum prothrombin conversion accelerator (SPCA), cothromboplastin or stable factor	Zymogen of serine protease	Hepatocytes (in the presence of vitamin K)	Activated by factor III. Activates factors IX, X (involved in the formation of prothrombinase in external path)
<b>VIII: Antihemophilic factor A, antihemophilic globulin (AHG)</b>	Protein cofactor	Hepatocytes	Activated by thrombin. Creates optimal conditions for the interaction of factors IXa and X
<b>von Willebrand factor</b>	Structural protein	endotheliocyte, megakaryocyte	Stabilizes factor VIII. Promotes platelet adhesion
<b>IX</b> Christmas Factor, antihemophilic factor B, plasma thromboplastin component (PTC)	Zymogen of serine protease	Hepatocytes (in the presence of vitamin K)	Activated by factor IXa, VIIa. Activates factor X
<b>X</b> Stuart-Prower Factor	Zymogen of serine protease	Hepatocytes (in the presence of vitamin K)	Activated by factor VIIa and VIIIa. Is part of the active prothrombinase. Passes prothrombin to thrombin (IIa)
<b>XI</b> Plasma thromboplastin antecedent (PTA)	Zymogen of serine protease	Hepatocytes	Activated by factor XIIa. Activates factor IX
<b>XII</b> Hageman Factor or contact factor	Zymogen of serine protease	Hepatocytes	Activated by kallikrein and HMWK. Starts the intrinsic pathway of blood coagulation. Activates the PPK, system of fibrinolysis
<b>XIII</b> Protransglutaminase, fibrin stabilizing factor (FSF), fibrinolygase	Zymogen of transglutaminase	Hepatocytes, megakaryocyte	Activated by thrombin and $\text{Ca}^{2+}$ . Stabilizes fibrin. Promotes tissue repair
<b>Plasma prekallikrein (PPK) or Fletcher factor</b>	Zymogen of plasma kallikrein	Hepatocytes	Activated by HMWK, factor XIIa. Activates factor VII, XII, HMWK, plasminogen
<b>Fitzgerald factor or high molecular weight kininogen (HMWK)</b>	Glycoprotein	Hepatocytes	Activates factor XI, XII plasminogen, PPK

### The mechanism of vascular-platelet hemostasis

Activation of vascular-platelet (primary) hemostasis makes a complete stop of bleeding from capillaries and venules and temporary stop of bleeding from veins, arterioles and arteries by forming the primary hemostatic plug from which upon activation of the secondary (coagulation) hemostasis formed thrombus.

Key mechanisms of thrombosis are: damage of vascular endothelium; local vasoconstriction; adhesion of platelets to the site of naked subendothelium; platelet aggregation; activation of blood clotting while reducing its lytic properties.

### ***1. Damage of endothelium and the primary vasospasm***

Microvessels respond to damage by short-term spasm, causing them bleeding does not occur in the first 20-30 seconds. Reflex spasm of blood vessels by contraction of smooth muscle cells of the vascular wall and supported by vasospastic agents secreted by the endothelium and platelets (serotonin, TxA<sub>2</sub>, norepinephrine, and others).

Endothelial damage is accompanied by a decrease in of the vascular wall and thromboresistance naked subendothelium that contains collagen and expresses the adhesion proteins - von Willebrand factor, fibronectin, thrombospondin.

### ***2. The adhesion of platelets to the site of naked subendothelium***

Carried out in the first few seconds after endothelial damage due to:

- reducing the amount of surface negative charge of the vascular wall in violation of its integrity;
- platelets receptor to collagen.

The stabilization of the resulting compound is carried adhesion proteins - von Willebrand factor, fibronectin and thrombospondin, forming "bridges" between their complementary platelet glycoprotein and collagen.

### ***3. Activation of platelets and secondary vasospasm***

The activation of platelets is caused by thrombin that formed from prothrombin under the influence of tissue thromboplastin, PAF, ADP (released together with thromboplastin at the vascular wall damage), Ca<sup>2+</sup>, adrenaline.

The process of platelets activation is associated with the chemical modification of membranes and induction of enzyme glycosyltransferase, phospholipase A<sub>2</sub> in them. Glycosyltransferase interacts with specific receptor on the molecule of collagen and thereby provides "landing" of platelets on the subendothelium.

Phospholipase A<sub>2</sub> starts the hydrolysis of phosphatidylethanolamine, that lead to the release of arachidonic acid. From arachidonic acid by the action of COG formed prostaglandins PgG<sub>2</sub>, PgH<sub>2</sub>, that transforming to the TxA<sub>2</sub> (a potent inducer of platelet aggregation and vasoconstrictor) under the influence of an enzyme thromboxane synthetase. Prostaglandins contribute to the accumulation of cAMP in platelets, regulate protein phosphorylation and activation of calmodulin, that transporting Ca<sup>2+</sup> from the dense tubular system of platelets into the cytoplasm. As a result, there is an activation of contractile protein of actomyosin complex, which is accompanied by a contraction of microfilaments of platelets with the pseudopodia formation. This further enhances platelet adhesion to the damaged endothelium.

At the same time, by the Ca<sup>2+</sup>-induced contraction of microtubules occurs emptying of granules at two phases: the first phase – release the contents from dense granules, the second – α-granules. TxA<sub>2</sub> and dismissed from the dense granules of platelets vasoactive substances cause secondary vasospasm.

### ***4. Platelets aggregation***

During degranulation of platelets are released TxA<sub>2</sub>, ADP, serotonin, β-thromboglobulin, platelet factor 4, fibrinogen and others components of dense granules and α-granules. They cause sticking of platelets together and with collagen. In addition, the appearance of the paf in the bloodstream (at endothelial destruction) and components of platelet granules leads to the activation of intact platelet, their aggregation with platelets that adherent on the endothelium.

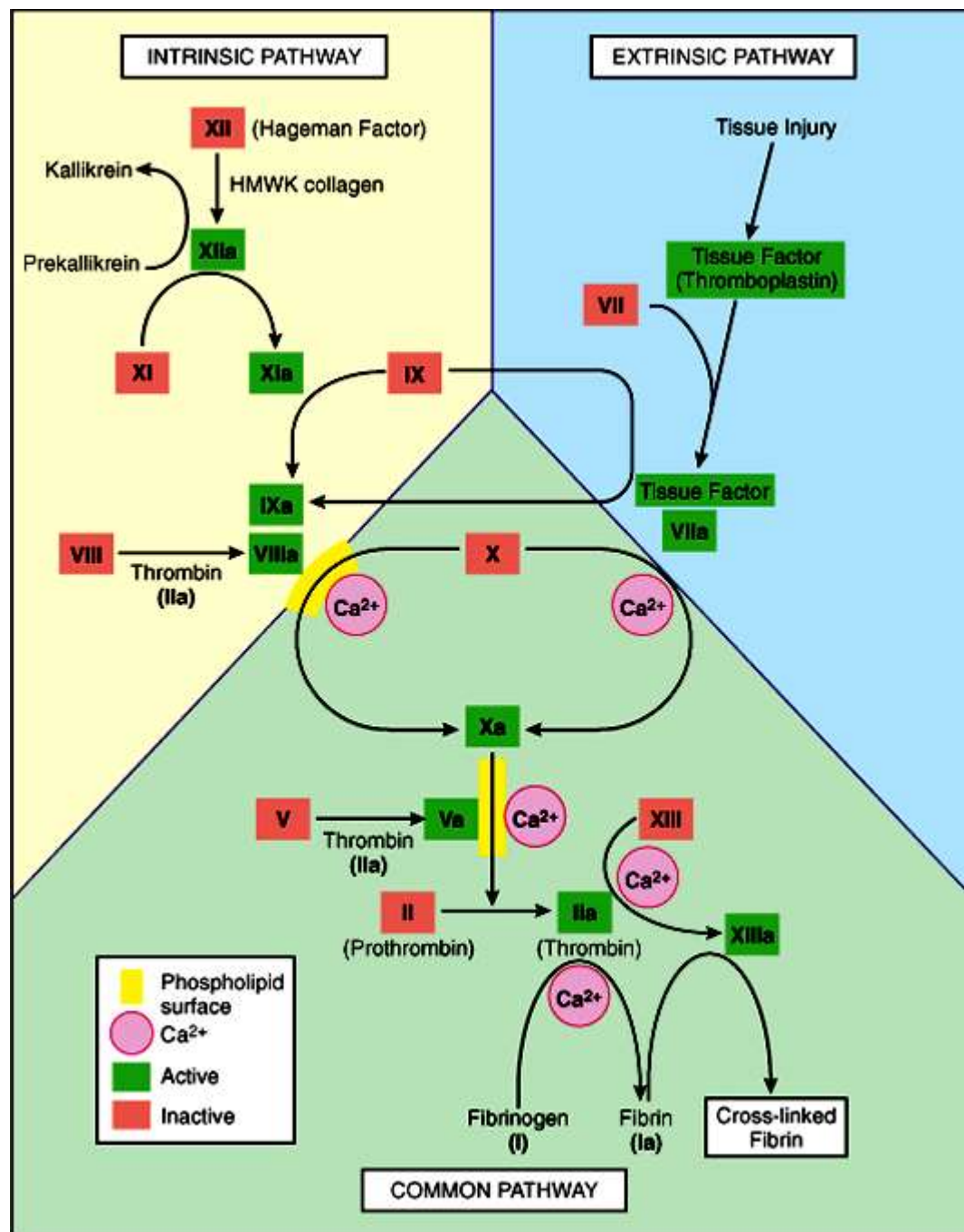
Platelets aggregation does not develop in the absence of extracellular Ca<sup>2+</sup>, fibrinogen.

### ***5. The formation of hemostatic plug***

As a result of platelet aggregation formed primary (temporary) hemostatic plug that obturate vascular defects (does not contain fibrin). Subsequently, on the surface of platelets aggregate adsorbed plasma coagulation factors and starts the "internal cascade" of coagulation that ends by the precipitation of stabilized fibrin fibers and the formation of platelet plug on the basis of a blood clot (thrombus).

At contraction of platelets thrombosthenin the thrombus compacted (clot retraction).

"External cascade" of blood clotting involves the release of tissue thromboplastin. Additionally, platelets can independently (in the absence of contact factors) start of blood clotting by the interaction of the factor Va (exposed on their surface) with factor Xa of plasma, catalyzes the conversion of prothrombin to thrombin.



**Figure 6 – Scheme of hemostasis (Kumar V. et al., 2010)**

### **The mechanism of coagulation hemostasis**

There are three stages of the blood clotting process. The first stage ends with the formation of active prothrombinase complex on membrane phospholipids, which includes factors X, V, and  $\text{Ca}^{2+}$  by internal and external mechanisms. The second stage is characterized by the formation of thrombin (the active form of factor II). In the third stage (final phase of blood clotting) there is a formation and stabilization of fibrin clot.

Normal hemostasis is attained by cooperation and interaction of primary (vascular platelet) and secondary (coagulation) mechanisms of hemostasis impairments. Causes of hemostasis impairments are hereditary and acquired.

### **Regulatory Mechanisms**

Several inhibitory mechanisms prevent activated coagulation reactions from amplifying uncontrollably, causing extensive local thrombosis or disseminated intravascular coagulation. These mechanisms include

- inactivation of coagulation factors:
- fibrinolysis
- hepatic clearance of activated clotting factors

#### **Inactivation of coagulation factors:**

The liquid state of the blood is maintained due to its movement (lowering the concentration of the reactants), the adsorption of the coagulation factors by the endothelium, and independently synthesized and constantly founded in blood the primary anticoagulants (Table 20).

Table 20. Primary anticoagulants and mechanisms of their action

<b>Name</b>	<b>Mechanism of Action</b>
inhibitor of external coagulation pathway	inhibits "PF + VIIa + Xa + Ca <sup>2+</sup> " complex
$\alpha_2$ -macroglobulin	synthesized by hepatocytes inhibitor of "PF + VIIa» complex, thrombin, plasmin, kallikrein
$\alpha_1$ -antitrypsin	synthesized by hepatocytes inhibitor of trypsin, thrombin, plasmin, kallikrein, has to 90-92% of the total anti-protease activity of plasma.
thrombomodulin	receptor protein of endothelial cells, binds and inactivates thrombin; complexed with thrombin activates protein C and S
antithrombin III	neutralizes thrombin, factor Xa and IXa; plasma heparin cofactor
heparin cofactor II	forms a complex with heparin; active in the plasma devoid of antithrombin III
heparin	being a component of the vascular wall, activates antithrombin III, in a complex with antithrombin III inhibits thrombin stimulates release of inhibitor of external coagulation pathway by endothelial cells
protein C	synthesized by hepatocytes vitamin K-dependent inhibitor of factors Va and VIIIa (when activated by thrombin and complex «thrombomodulin+thrombin» in interaction with protein S) stimulates fibrinolysis (endogenous plasminogen activator)
protein S	synthesized by hepatocytes vitamin K-dependent Protein C cofactor involved in the proteolytic degradation of factors Va and VIIIa
inhibitors of fibrin monomers polymerization	inhibit the fibrin polymerization

Many of clotting factors and their fragments, formed during coagulation, act as secondary anticoagulants. In particular, the anticoagulant effects have fibrin and degradation (by plasmin) products of fibrinogen, inhibiting the final phase of blood coagulation. In pathological conditions in the blood may occurs immune inhibitors of blood coagulation factor in high titer – antibodies to factor VIII, IX etc. and to the membrane phospholipids, on which clotting factors is interact and activates.

#### **Fibrinolysis:**

Fibrin deposition and lysis must be balanced to maintain temporarily and subsequently remove the thromb during repair of an injured vessel wall. The blood fibrinolytic system comprises an inactive proenzyme, plasminogen, that can be converted to the active enzyme, plasmin. Plasmin degrades fibrin into soluble fibrin degradation products, by two physiological plasminogen activators (tissue and urokinase type). Plasminogen activators cleave plasminogen (from plasma) into plasmin. Plasmin proteolyze fibrin into soluble fibrin degradation products. They are swept away in the circulation. Fibrinolysis is controlled by inhibitors of plasminogen activator and plasmin inhibitors (eg,  $\alpha_2$ -antiplasmin).

#### **Classification of hemostasis disorders:**

***By pathogenesis:***

- change in quantity and properties of thrombocytes
- coagulopathias
- vasopathia

***By the character of impairments:***

- hypocoagulative ( hemorrhage syndrome);
- hypercoagulative (thrombotic syndrome);
- complex impairments (thrombotic-hemorrhage conditions)

Reasons for hypocoagulation are united in four groups:

- thrombocytopenia
- thrombocytopathy
- vasopathy (angiopathy)
- coagulopathy

**CHANGE IN QUANTITY AND PROPERTIES OF THROMBOCYTES**

In normal platelet count is  $150-450 \times 10^9/l$ . Violations of platelet hemostasis include:

- thrombocytopenia
- thrombocytosis
- thrombocytopathy

**Thrombocytopenia**

*Thrombocytopenia* – is a decrease in the number of thrombocytes below  $150 \times 10^9/l$ . Hemorrhagic syndrome depends on degree of thrombocyte number decrease. Clinical signs of thrombocytopenia are manifested in the decrease of thrombocytes number below  $50 \times 10^9/l$  and include: gum bleeding, menorrhagias, the increased ability of incutaneous bleedings, and appearance of petechias of different localization. There are gastric and nasal bleedings in severe cases.

***Classification of thrombocytopenia***

- independent disease
- symptoms of various diseases:

- hereditary
- acquired

***Mechanisms of heredity thrombocytopenia:***

- insufficient number of megakaryocytes in BM (Fanconi syndrome, cyclic amegakaryocytic thrombocytopenia);
- inefficient thrombocytopoiesis;
- defect of synthesis of thrombopoietin;
- megakaryocyte dystrophy syndrome ("gray" platelet anomaly Mey-Hegglin).

***Mechanisms of acquired thrombocytopenia:***

**1. Decreased intensity of production in BM:**

- hypo-or aplasia of hemopoiesis
- IR, chemical substances
- substitution BM by tumor tissue
- inefficient thrombocytopoiesis

**2. Increased of thrombocytes destruction out of BM:**

- immune:
  - ✓ transimmune (through placenta in Verlgof disease)
  - ✓ heteroimmune (Ab to hapten fixed on thrombocytes)
  - ✓ isoimmune (incompatibility by Ag of mother and fetus thrombocytes or donor and recipient during hemotransfusions)
  - ✓ autoimmune (idiopathic, with lymphoproliferative disease)
- non-immune:

- ✓ syndrome of hypersplenism
- ✓ mechanical trauma of thrombocytes (catheters, prosthetic heart valves)

3. Increased consumption of thrombocytes:

- consumption coagulopathy (HUS, ITP, hemorrhagic vasculitis)
- thrombophilia

4. Dilution

5. Redistribution

Decreased production of platelets is caused by the impairment of thrombocyte formation. In patients with vitamin B<sub>12</sub> or folic acid deficiency, there is accelerated destruction of megakaryocytes, in the bone marrow (ineffective megakaryopoiesis) because DNA synthesis is impaired. It is observed in case of bone marrow inhibition by cytotoxic drugs, radiation, thiazides, estrogens, alcohol, in bone marrow infiltration in leukemia, disseminated cancer.

Consumption develops in case of the increased platelet utilization above the bone marrow compensatory possibility. This is a cause of thrombocytopenia developing by immunologic and non-immunologic mechanisms. Immunologic destruction: thrombocytopenic purpura in children and adults, neonatal alloimmune purpura. Nonimmunologic destruction: DIC, sepsis, endothelial injury by viruses.

Dilution develops in massive fluids transfusions after severe blood loss.

Redistribution is observed in patients who have a marked splenomegaly and an increase in platelet pool of spleen.

***Manifestations of thrombocytopenia***

Bone marrow:

- Hyperplasia with an increase in the number of megakaryocytes and megakaryoblasts (with increased destruction or generalized "consumption" of platelets)
- Hypoplasia (in patients with leukemia, radiation sickness, tumor metastasis in bone marrow)
- Decrease in glycogen content and activity of LDH, G-6-PD in megakaryoblasts and megakaryocytes, which reduces the life span of platelets

Peripheral blood:

- Reduction of the platelets number and an increase in their size, generally normal RBC, Hb, WBC count.
- In patients with severe hemorrhagic syndrome may develop anemia.

**Thrombocytosis**

Thrombocytosis – characterized by an increase in the number of platelets per unit volume of blood above  $450 \times 10^9/l$ .

***Thrombocytosis divided into:***

- primary (tumor, essential),
- secondary (reactive);
  
- absolute,
- relative;
  
- symptomatic,
- idiopathic.

Primary thrombocytosis – arise from malignant transformation of megakaryoblasts or hematopoietic stem cells with the subsequent intensification thrombocytopoiesis (CML, AML, erythremia, essential thrombocythemia).

Secondary thrombocytosis – result from increasing the concentration or activity the stimulants of thrombocytopoiesis: thrombospondin, thrombopoietin, PAF, IL-3, IL-6, IL-11; genesis is not associated with damage to hematopoietic cells. Develop after massive bleeding, after splenectomy in chronic inflammation of various etiologies (rheumatoid arthritis, osteomyelitis, tuberculosis), hypercortisolism and stress.

Absolute – are characterized by an increase in the number of platelets in the blood as a result of their increased formation.

Relative – does not accompanied by an increase in the number of blood platelets:

- Redistributive (increase in the number of platelets in the areas of microvessels with damaged walls, due to the ejection of blood from the depot and exit from bone marrow);
- Hemoconcentration (due to dehydration).

Symptomatic – a symptom of myeloproliferative diseases (chronic myeloid leukemia, erythremia, myelofibrosis, acute leukemia megacaryoblastic et al.).

Idiopathic – an independent nosological form (essential thrombocythemia).

***Manifestations of thrombocytosis:***

Thrombotic syndrome – excess blood clots with significant thrombocytosis.

Hemorrhagic syndrome – occurs in leukemia along with thrombosis/ due to platelets tumor clones may be functionally defective. Also hemorrhagic syndrome may develop compensatory through increased anticoagulant activity and fibrinolysis

## **Thrombocytopathia**

**Thrombocytopathy** – pathological conditions characterized by platelet dysfunction. Unlike thrombocytopenia, thrombocytopathia is characterized by stable functional, biochemical and morphologic changes in platelets and normal platelet count.

### ***Classification of thrombocytopathia***

- Hereditary (primary):
  - ✓ Glanzmann thrombasthenia;
  - ✓ Von Willebrand disease;
  - ✓ Bernard-Soulier disease;
- Acquired (secondary) or symptomatic:
  - ✓ in diseases and syndromes (leukemia, liver and kidney diseases, lack of vitamins B<sub>12</sub>, C);
  - ✓ iatrogenic (under the influence of medicines).

***Pathogenesis*** of thrombocytopathy includes violation:

- the synthesis and accumulation of BAS in platelets granules
- degranulation and release of platelet factor in the blood plasma
- the structure and properties of the platelet membrane

### **Glanzmann thrombasthenia**

Glanzmann thrombasthenia is a rare autosomal recessive bleeding syndrome affecting the megakaryocyte lineage and characterized by lack of platelet aggregation.

Etiology: absence or defect in the membrane receptor for fibrinogen and glyco-proteins IIb-IIIa.

Pathogenesis: reduction in the intensity of fibrinogen binding to the membrane of thrombocytes, violation of thrombocytes aggregation.

Manifestations:

- petechial ecchymoses bleeding type
- a tendency to bleeding from the mucous membranes (nasal, uterine, hemorrhage in sclera and retina)
- prolonged bleeding after tooth extraction, surgical manipulations.

## **COAGULOPATHY**

Coagulopathy are hereditary (hemophilia A, B, C, Von Willebrand disease et al.) and acquired (DIC syndrome). Among the hereditary bleeding disorders dominate (about 97%) haemophilia A and B.

### **Hereditary coagulopathy**

#### **Hemophilia A**

Etiology: a deficiency of factor VIII (antihemophilic globulin). Inherited X-linked recessive affected male persons (10 per 100 thousand men)

Pathogenesis: deficiency leads to a sharp increase in the time of formation of the prothrombinase complex, which is accompanied by a long, almost does not stop bleeding with minor vessels trauma (biting tongue, bruises).

Manifestations:

It is characterized by hematoma type of bleeding. In mild form of disease the bleeding are possible only when significant trauma or surgical interventions, is subclinical and often not diagnosed. In severe or very severe form is manifested from newborns and first years of life in children. Recurrent bleeding in the large joints (hemarthrosis) lead to ankylosis. Large inter- and intramuscular, retroperitoneal hematoma with subsequent destruction of the soft tissues, severe and frequent spontaneous bleeding, persistent recurrent gastrointestinal bleeding and kidney.

**Hemophilia B (Christmas disease)**

Etiology: a deficiency of factor IX (Christmas factor). Inherited X-linked recessive.

Pathogenesis: defect leads to a significant slowdown in the formation of the prothrombinase complex that lead to the development of hematoma type of bleeding.

Manifestations:

The clinical picture is characterized by bleeding (hemarthrosis, hematomas), but their frequency is 5 times lower than in the deficiency of factor VIII.

**Hemophilia C**

Etiology: a deficiency of factor XI (plasma thromboplastin antecedent). Inherited as an autosomal recessive.

Pathogenesis: isolated violation of the internal mechanism of blood coagulation.

Manifestations:

In heterozygotes bleeding is minor.

Homozygotes have a few complications associated with bleeding, but the injury or surgery may cause severe bleeding and formation of hematoma and hemarthrosis.

**Parahemophilia (Owren's disease)**

Etiology: a deficiency of factor V (proaccelerin, labile factor, accelerator, globulin). Inherited as an autosomal recessive and autosomal dominant.

Manifestations:

The disease is characterized by hemorrhagic syndrome: marked petechiae, ecchymoses, bruising, nasal, gingival, gastrointestinal bleeding, menorrhagia. In patients with severe forms of the disease is often prolonged bleeding after tooth extraction, trauma, cuts.

**Female hemophilia**

Female hemophilia meets very seldom (described 50 cases). It is a genetically heterogeneous disease. The main variants of female hemophilia:

- normal chromotype (XX) and double inheritance of true hemophilia – appears in girls whose fathers have hemophilia and mothers are carriers of disease (often incest);
- normal chromotype (XX) and one sided hemophilia inheritance;
- incomplete chromotype with one X-chromosome (XO). These patients may have severe hemophilia form, as men from this family;
- in «women» with testicular feminization (XY);
- autosomal-dominant forms of factor VIII deficiency (in this group should be excluded von Willebrand disease).

**Von Willebrand disease**

Etiology: Von Willebrand disease is the most common inherited disorder of bleeding (autosomal-dominant type of inheritance). This disease is revealed in both sexes.

Pathogenesis: deficiency of Von Willebrand factor leads to the violation of thrombocytes adhesion to collagen of vascular wall and decrease the intensity of the formation of complex vWF-Factor VIII. In the absence of vWF, the factor VIII is subjected to accelerated destruction in the blood. A result is

deficiency of factor VIII and related spontaneous hematoma bleeding. Thus, von Willebrand's disease characterized by impaired platelet and coagulation hemostasis.

#### Manifestations

Clinically it is manifested by bleedings into the skin and mucose membranes: nasal bleedings, ecchymoses, menorrhagies, hematuria, severe bleedings from a slight traumas or surgical wounds (in tonsillectomy, tooth extraction). Patients with von Willebrand disease have prolonged bleeding time with normal platelet count and also prolonged partial thromboplastin time.

### **Acquired coagulopathies**

#### **Disseminated intravascular coagulation syndrome (DIC syndrome)**

DIC – nonspecific syndrome characterized by disseminated intravascular coagulation of blood proteins, aggregation of formed elements, activation and depletion of components coagulation and fibrinolytic systems, blockage of microcirculation blood vessels in organs followed microthrombogenesis.

#### ***Classification***

##### By clinical course:

- acute
- subacute
- chronic

##### By process localization:

- disseminated intravascular clotting (the organism level)
- localized intravascular clotting (in organ or part of organ limits)

##### By severity:

- compensated
- subcompensated
- decompensated

#### ***Etiology:***

- all kinds of shock, trauma (for example, crush syndrome)
- terminal states
- obstetric syndromes (placenta, amniotic fluid embolism, atonic uterine bleeding, fetal death etc.)
- massive destruction and necrosis in organs (burns, frostbite, pancreatic necrosis, destructive pneumonia)
  - traumatic surgery
  - acute intravascular hemolysis (transfusion of incompatible blood transfusion and massive) and chronic hemolysis (hemolytic anemia)
    - severe infection and sepsis
    - persistent bacterial and viral infections
    - malignant tumors and hemoblastoses
    - dehydration
    - massive blood contact with a foreign surface (extracorporeal circulation, chronic hemodialysis)
    - damage of the endothelium (dissecting aortic aneurysm, progressive atherosclerosis, systemic lupus erythematosus, rheumatoid arthritis, hemolytic uremic syndrome, acute glomerulonephritis, fever, allergic reactions)

#### ***Pathogenesis of DIC-syndrome:***

- initial activation of coagulation system and thrombocytes by endogenous factors: tissue thromboplastin, leukocytic proteases, products of tissue destruction, tumoral procoagulants;
- long-lasting thrombinemia with the increased level of its markers in blood;

- depletion of anticoagulant with the decreased level of antithrombin III, protein C, plasminogen and the increased level of thrombomodulin;
- systemic endothelial injury and the decrease in its antithrombotic potential;
- formation of micro blood clots and block of microcirculation in target-organs (a brain, adrenal glands, a liver, kidneys, an intestine, a stomach) with dystrophy and destruction on these organs;
- activation of fibrinolysis in a zone of microcirculation block and its release exhaustion in blood circulation;
- consumption of coagulation factors and consumption thrombocytopenia (and thrombocytopeny), leading to bleeding and systemic hypocoagulation terminal until full incoagulability blood (hemorrhagic phase syndrome);
- violation of the barrier function of stomach and intestines mucous membrane with impairment of their barrier function and transformation of aseptic DIC-syndrome into the septic;
- secondary severe endogenous intoxication.

#### ***Stages of DIC-syndrome:***

- hypercoagulation and thrombogenesis (short);
- consumptive coagulopathy (characterized by higher consumption and depletion of clotting factors and thrombocytes, hypofibrinogenemia and deficiency of anticoagulants);
- hypocoagulation (hypocoagulation-hemorrhagic phase) manifested by hemorrhagic syndrome;
- reparative (residual thrombosis and vascular blockade).

#### ***Manifestations:***

DIC is characterized by symptoms of multiple organ failure as a result of injury and dysfunction of target organs:

1. Acute pulmonary insufficiency (up to pulmonary distress syndrome).
2. Acute renal or hepatorenal insufficiency (decreased urine output and uremia).
3. Cerebral symptoms associated with cerebral ischemia.
4. The damage of gastric and intestinal mucosa (heavy bleeding, acute hypoxic ulcers, impaired barrier function of the mucous membrane and transformation of aseptic DIC into the septic toxic form).
5. Adrenal or pluriglandular endocrine insufficiency hemodynamically unstable.
6. Systemic inflammatory response syndrome with accumulation of cytokines and other metabolites in the blood.

#### **The main sub-syndromes observed in DIC:**

*Transformation of aseptic DIC-syndrome into septic.* It is mostly associated with infection of the tissue damaged loci or barrier function impairment of intestinal mucose membrane with the subsequent massive entrance of bacterial population in blood. It is presented by fever, leukocytosis with nuclear shift to the left, the increased ESR, the increased level of acute phase proteins (C reactive protein), interleukins. Participate in the development of terminal hemorrhagic syndrome.

*Sub-syndrome of respiratory failure.* Respiratory symptoms such as dyspnea, cyanosis and respiratory difficulty may dominate in the bleeding of DIC. Sub-syndrome of respiratory failure needs in controlled ventilation.

Sub-syndrome of acute renal and hepatorenal insufficiency. It is often needs in hemodialysis and plasmapheresis.

*Sub-syndrome of the impairment and injury of other organs* (adrenal glands, brain, heart) forms the poly-organic insufficiency syndrome.

*Sub-syndrome of the stomach and intestine injury* has three clinical manifestations: bleeding erosion and ulcer formation (shock or hypoxic ulcers), diffuse bleedings of mucosal membrane barrier function impairment with transformation of aseptic DIC into septic.

## **VASSOPATHY (ANGIOPATHY)**

Vasopathies (angiopathies) are the diseases, which are characterized by the bleeding in the result of vascular wall pathology.

### ***Etiology***

Etiological factors may be exogenous (physical, chemical and biological) or endogenous (immunological, genetic), acquired and genetic.

The acquired forms develop as a result of ionizing radiation, deficiency of vitamin C (results in reduction of collagen synthesis), side effect of medicines, viral infection, various factors, which cause inflammation of vessels, including immune factors (autoimmune aggression against endothelium), disorder of vascular trophism, destruction of vascular walls as a secondary effect of leukemic infiltrates, disorder of the nervous and hormonal regulation of vascular tonus.

Genetic forms is a result of the mutations of genes, which are responsible for synthesis of endothelial proteins (enzymes, collagen, contractile proteins and other) and receptors

### ***Pathogenesis***

Damage of the vessels under exogenous and endogenous factors results in inflammation and impairment of endothelium participation in hemostasis (hemorrhagic vasculitis). Endothelium loses ability for production of active substances (prostaglandins, procoagulants) with results of disorders of the thrombocyte-vascular hemostasis. There occurs predisposition to bleeding.

Congenital angiopathies are presented by telangiectasia (arteriovenous aneurysms with subendothelial maldevelopment and lack of collagen), hemangioma (vascular tumor).

## THROMBOPHILIC STATE

**Thrombophilia** is an inherited or acquired disorders of hemostasis mechanism predisposing to early emergence and recurrence of thrombosis and obliteration of blood vessels, ischemia and infarctions of organs.

Thrombophilia is divided into a number of major groups:

- hemorheological form (hemoconcentration, increased viscosity (dehydration, hyperfibrinogenemia paraproteinemia), Ht, Hb, RBCs (polycythemia vera), changes in the shape and deformability of RBCs (hereditary hemolytic anemias);
- vascular and thrombocyte disorders of hemostasis due to:
  - ✓ significant increase in thrombocytes level in blood (up  $1200 \times 10^9/l$ ),
  - ✓ increase in adhesiveness and aggregation of thrombocytes (viscous platelets syndrome, atherosclerosis, diabetes mellitus, taking hormonal contraceptives, etc.),
  - ✓ overproduction of vWF;
- hereditary or acquired deficiency or abnormalities of anticoagulants;
- overproduction or hereditary abnormal plasma coagulation factors (factors lose their sensitivity to physiological anticoagulant or fibrinolytic system components);
- genetically or acquired disorders of fibrinolysis (decreased tissue plasminogen activator or increased plasma levels of its inhibitors, deficiency or abnormality of plasminogen);
- thrombophilia with metabolic origin (decrease in antithrombotic potential of endothelium and complex disorders in all links of hemostatic system: in atherosclerosis, hyperlipidemia, hyperhomocysteinemia, diabetic angiopathy etc.);
- autoimmune and infectious-immune thrombophilia (antiphospholipid syndrome);
- paraneoplastic thromboembolic syndromes (thrombotic complications in all cancer types (visceral forms) in surgical operations and chemotherapy);
- iatrogenic (medical) forms (in catheterization and surgical operations of heart and vessels, vessel and valve replacement, in bone marrow stem cell transplantation, drug-induced forms);
- complex forms of thrombophilia (presents two or more impairments).

The most known forms of thrombophilia are hyperhomocysteinemia and antiphospholipid syndrome.

## SYNDROME IN HEMOSTATIC DISORDERS

Violation of the hemostatic system is characterized by hemorrhagic and thrombotic syndromes.

### **Hemorrhagic (manifested by bleeding)**

Distinguish the following types bleeding:

**Capillary or microcirculatoric (petechia-bruise) type of hemorrhage.** It is characterized by the appearance of small painless pointed or spotted hemorrhages on the skin. Hemorrhages are often associated with menorrhagias, gum bleeding, rarely with the retina hemorrhage and gastric bleedings. Hemorrhages are easily provoked by mechanical traumas of microvessels. This hemorrhage type is characteristic of thrombocytopenia and thrombocytopathia, von Willebrand disease, prothrombin complex factor insufficiency (VII, X, V, II), some hypo- and disfibrinogenemias, moderate overdosage of anticoagulants. The bruise type of hemorrhage is often admitted in hereditary thrombocytopathias; the petechial type of hemorrhage is not characteristic.

**Hematoma.** It is characterized by painful strained hemorrhages in subcutaneous cellular tissue, muscles, large joints, in peritoneum and retroperitoneal space. It may lead to nerve compression, joint destruction, bone tissue destruction, locomotor apparatus impairments. Renal and gastro-intestinal bleedings may develop.

Prolonged bleedings in wounds, tooth extractions, surgical operations may develop. It is observed in hereditary blood coagulation impairments (hemophilia A,B, excess insufficiency of factor VII), in hereditary thrombocytopathia with absence of thrombocytic factor 3, acquired coagulopathias associated with appearance of factors VIII, IX, VIII + V inhibitors in blood, in overdosage of anticoagulants.

**Complex capillary-hematoma type of bleeding.** It is characterized by petechial-bruise hemorrhages associated with numerous dense hemorrhages and hematomas. In the absence of joint and bone injury (unlike hematoma), bruises may be large and painful. This type of hemorrhage is observed in hereditary (excess insufficiency of VII and VIII factors, severe form of von Willebrand disease) and acquired impairments (acute, subacute DIC-syndrome, overdosage of direct and non-direct anticoagulants).

**Vasculitis purple type of hemorrhage.** It is characterized by the appearance of monomorphous papulous-hemorrhage on palpation. The eruption elements do not disappear on touch. Nephritis development and intestinal bleedings are possible. This type of hemorrhage is observed in infectious and immune vasculites.

**Angiomatous hemorrhage.** It is characterized by recurring local bleedings. It is observed in angiomas, arterial venular anastomoses, teleangioectasias (Rendu-Osler disease). Bleeding is associated with slight injury of vascular wall in angioectasia loci and decreased stimulation of adhesion and aggregation of thrombocytes in this area. There are three types of teleangioectasias: early – small irregular form spots; intermedial – vascular spiders; late (nodular) – bright red nodes 5–7 mm.

### **Thrombotic (manifested by thrombosis of different localization)**

Develops in the presence of the Virchow triad:

1. damage of vascular wall and of endothelium loss of thromboresistance;
2. the imbalance between the activity of coagulation, anticoagulation and fibrinolytic systems;
3. slowing blood flow.

### **Questions for self-control of knowledge:**

1. Define a concept of "homeostasis." What are mechanisms of hemostasis and what is physiological significance of hemostatic system?
2. Describe a vascular-platelet hemostasis. What is a function of platelets?
3. What is a mechanism of coagulation homeostasis? Name blood clotting factors. What are primary and secondary physiological anticoagulants?
4. Specify etiology and pathogenesis of hereditary coagulopathy.
5. What are etiology and pathogenesis of DIC syndrome? What are main clinical manifestations of DIC?

6. Describe pathology of platelet hemostasis: thrombocytopenia, thrombocytopathies, thrombocythemia. What are their etiology and pathogenesis?
7. What are principles of hemostatic disorders.

**Tasks for self-managed student work:**

1. Hemophilia. History of royal family.
2. Hereditary defects of membrane glycoproteins of platelets.
3. Acquired coagulopathies (DIC syndrome).

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