HEMORRHAGIC DIATHESES

ASPECTS OF
CLINICAL
AND LABORATORY DIAGNOSIS .
PRINCIPES OF TREATMENT.

Department of pediatrics

The physiologic role of hemostasis

- **Stopping of hemorrahge in the case of sanguine vessels lesion**
- **Recanalization of sanguine vessels in the case of accidental occlusion**
- **Maintaining of blood in liquid state in vascular lumen**

The components of Hemostasis System

- **Vascular wall**
- **Sanguine cells (thrombocytes, erythrocytes)**
- **Plasmatic factors of coagulation**
- **Activators and inhibitors of fibrinolytic system**
- **Anticoagulant factors**

Stages of hemostasis

- **Primary hemostasis**
  (white thrombocytary clot)
- **Secondary hemostasis**
  (red erythrocitary clot)
- **Fibrinolysis**
  (clot lysis)

Components of primary hemostasis

- **Vascular wall**
- **Thrombocytes**

Vascular endothelium
(anticoagulant function)

- Releasing of Prostacycline
- Producing of fibrinolysis tissular activator
- Ensuring the impossibility of contact activation
- Forming of anticoagulant potential

  Heparine + Antithrombine III
- Maintaining of dzeta-potential

Vascular endothelium
(procoagulant function)

- Tissular thromboplastin
- Stimulators of trhombocytary functions:

  adrenaline, noradrenaline, ADP
- Ensuring of activation through contact of thrombocytes and XII factor
- Synthesis of von Willebrand factor and other factors of coagulation
- Synthesis and releasing of A2 -Thromboxan

Thrombocytary functions

- **Angiotrophic**
- **Adhesivity**
- **Aggregation**
- **Synthesis, accumulation and releasing**
- **Contractibility**

Thrombocytary granules

- **α-Granules**
- **Dense granule**
- **Lisosomal granules**
- **Peroxisomes**

Components of α-granules

- **Von Willebrand factor**
- **Fibrinogen**
- **Factor V**
- **Factor P4 (antiheparinic)**

- **Protein S**

Components of dense granules

- **ADP**
- **Serotonin**
- **Calcium ions**
- **Adrenalin**
- **Antiplasmin**

- **ATP**

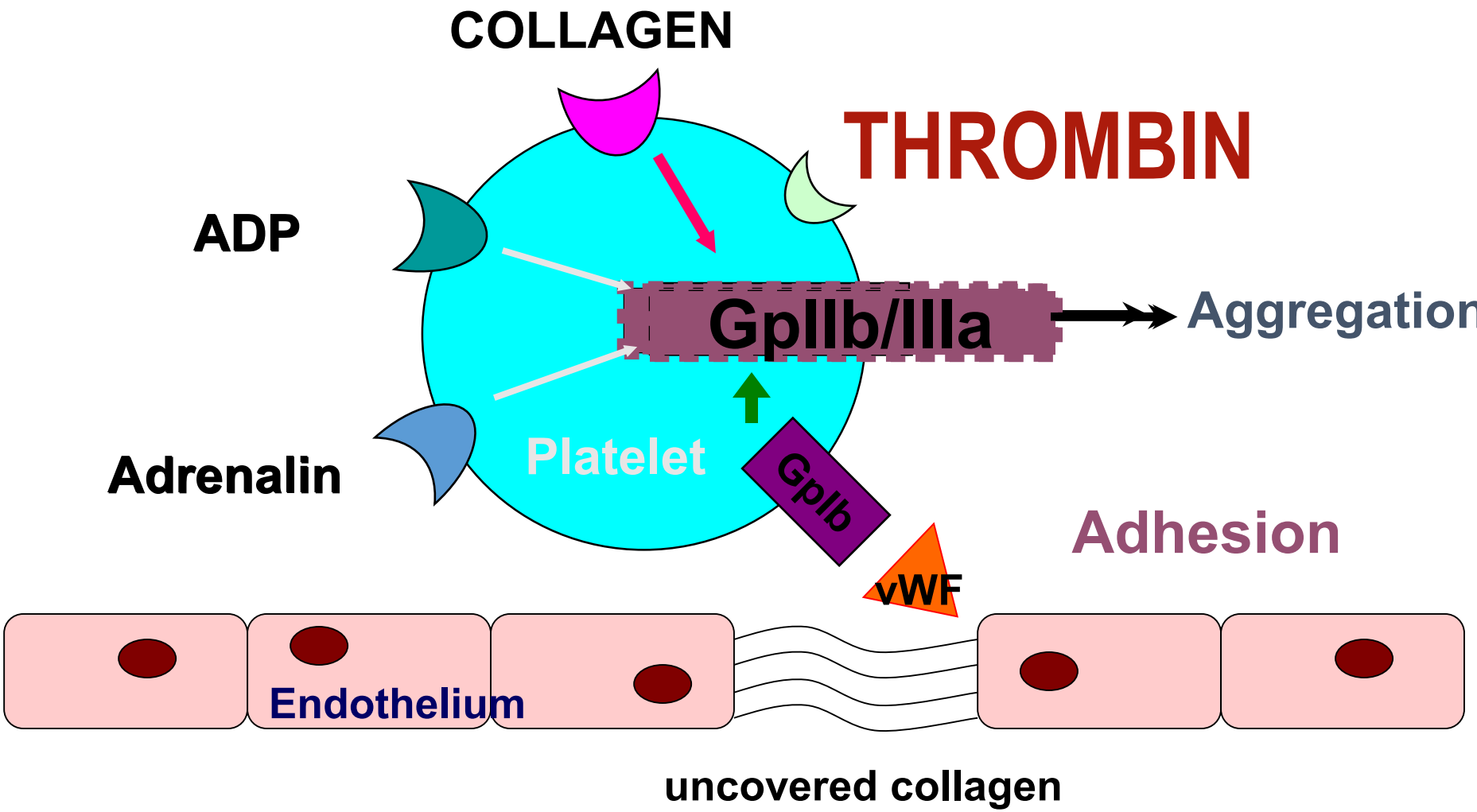
Thrombocitary factors

- **P1 – thrombocytary accelerator, identical to factor V of coagulation**
- **P2 – thrombin accelerator**
- **P3 – thrombocytary thromboplastin, partial thromboplastin**
- **P4 – antiheparinic factor**
- **P5 – coagulation factor, identical to fibrinogen**
- **P6 – thrombastenin**
- **P9 – fibrinstabilizer factor**
- **P10 – serotonin**
- **P11 – ADP**

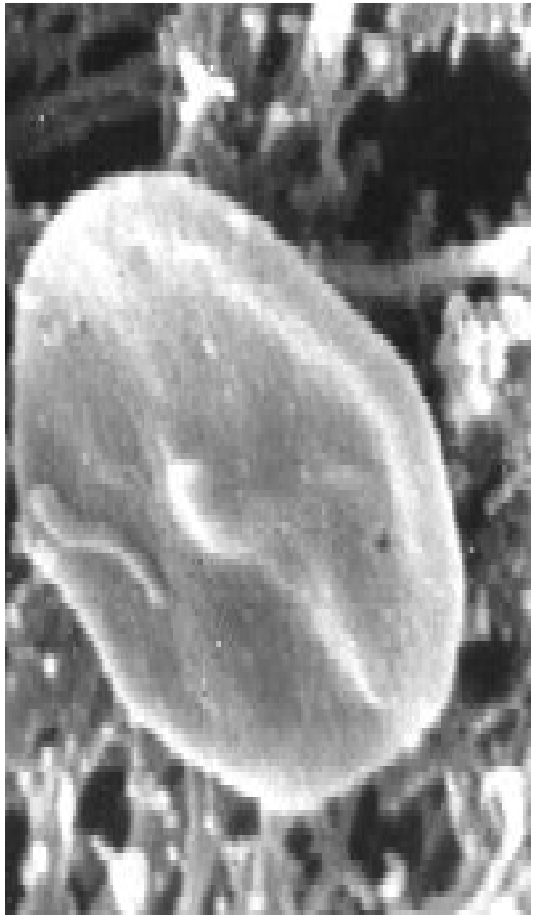
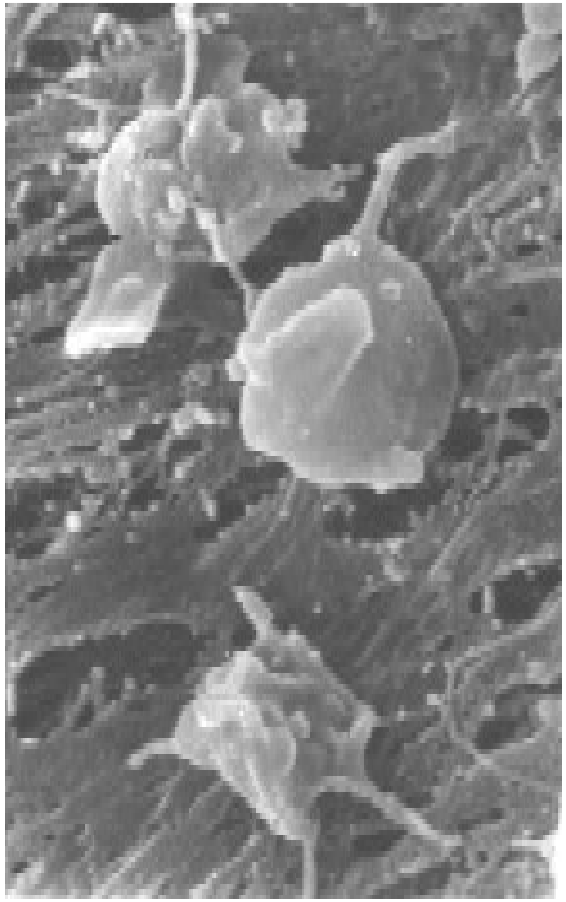
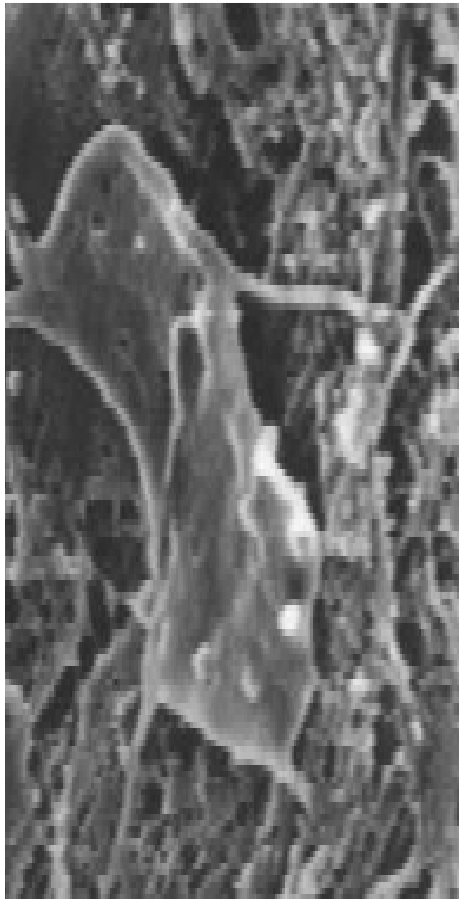
Thrombocytary activators

In vivo			In vitro
In normal		In pathology	
In affected vessel zone	In affected vessel	In blood	
ADP	Collagen	Proteolytic enzymes	ADP
Adrenalin	Von Willebrand factor	Antithrombocytary antibodies	Thrombin
Serotonin		Ag-Ac compexes	Collagen
Vasopressin		Bacteries	Adrenalin
Plasmin		Viruses	Ristomicin
v Willebrand factor		Tumoral cells	
Thrombin			

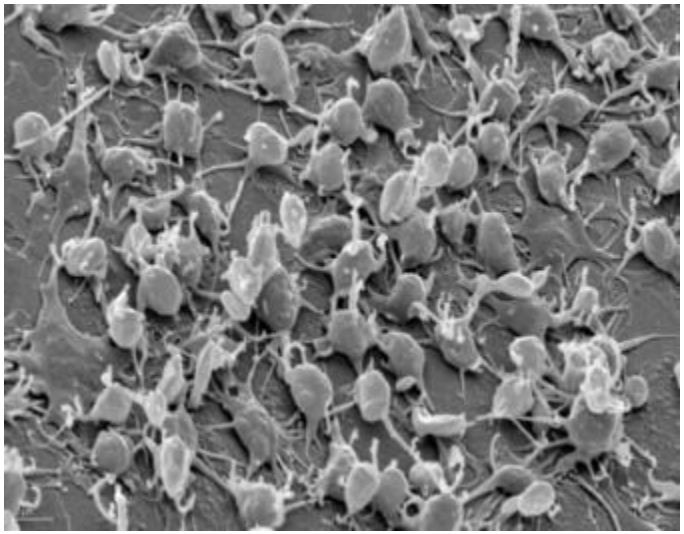
Thrombocytes activation



Thrombocytes
“in exercise of function”

Thrombocytes
“in exercise of function”



Secondary hemostasis. Plasmatic factors of coagulation

- **F I Fibrinogen**
- **F II Prothrombin**
- **F III Tissular thromboplastin**
- **F IV Ca++ ions**
- **F V, VI Proaccelerin, labile factor**
- **F VII Proconvertin, stabile factor**
- **F VIII Antihemophilic globulin**
- **F IX Plasmatic thromboplastin (F Cristhmas)**
- **F X Prothrombinase**
- **F XI Plasmatic thromboplastin predecessor**
- **F XII Factor of contact, f. Hagemann**
- **F XIII Fibrinstabilizer factor , fibrinase**

intrinsec pathway of coagulation

- **F XII**
- **F XI**
- **F IX**
- **F VIII**

- **F X a + F V + F IV**
  (prothrombinasic complex)

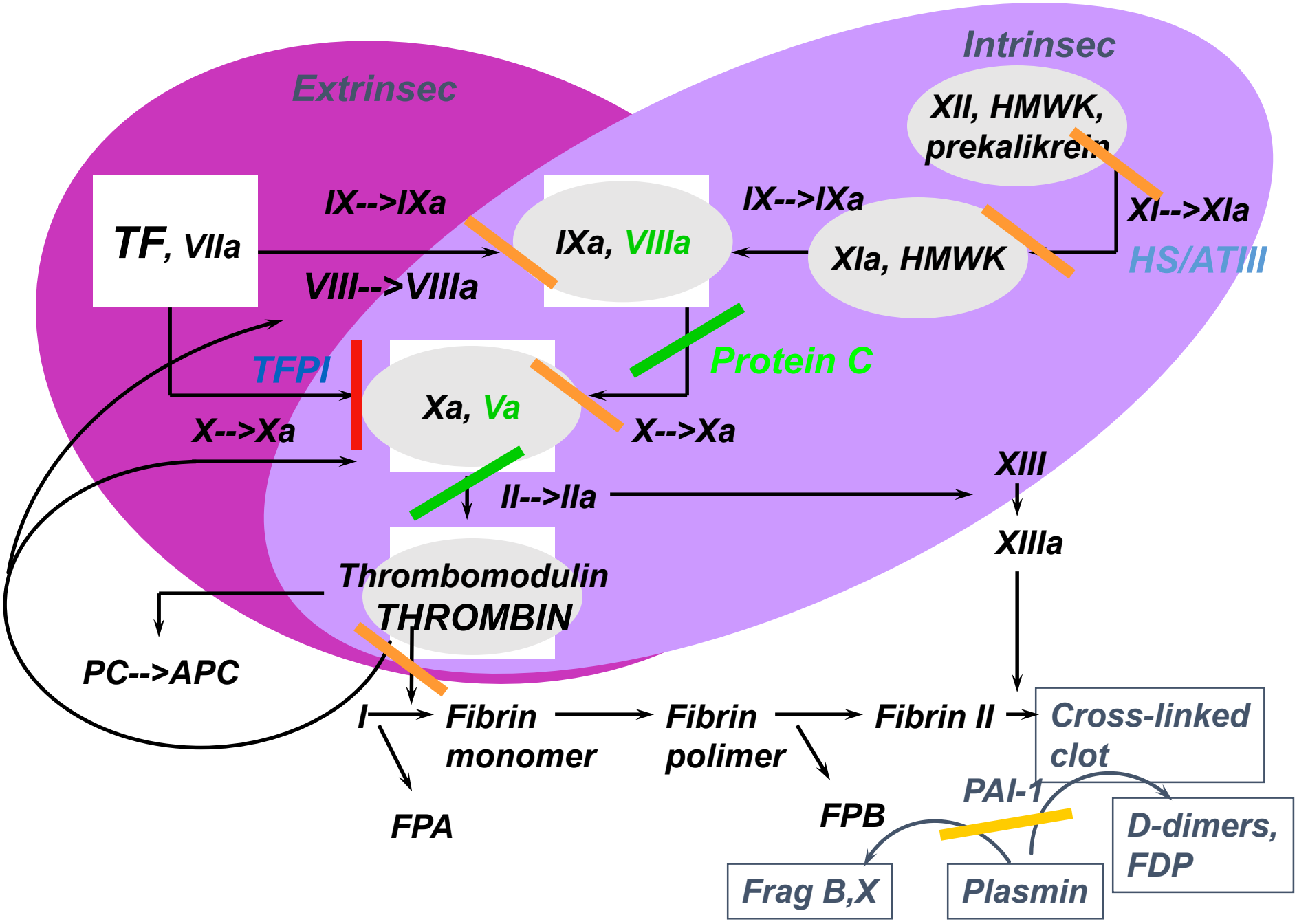
Extrinsec pathway of coagulation

- **F III**
- **F VII**

- **F X a + F V + F IV**
  (prothrombinasic complex)

commune pathway of coagulation

- **F X a + F V + F IV**
  (protrhombinasic complex)
- **F II (prothrombin – thrombin)**
- **F I (fibrinogen – fibrin)**


Extrinsec
Intrinsec
XII, HMWK, prekalikrein
TF, VIIa
IX-->IXa
IXa, VIIIa
IX-->IXa
XIa, HMWK
XI-->XIa
HS/ATIII
VIII-->VIIIa
TFPI
Protein C
Xa, Va
X-->Xa
X-->Xa
XIII
II-->IIa
XIIIa
Thrombomodulin
THROMBIN
PC-->APC
I
Fibrin monomer
Fibrin polimer
Fibrin II
Cross-linked clot
FPA
FPB
PAI-1
D-dimers, FDP
Frag B,X
Plasmin

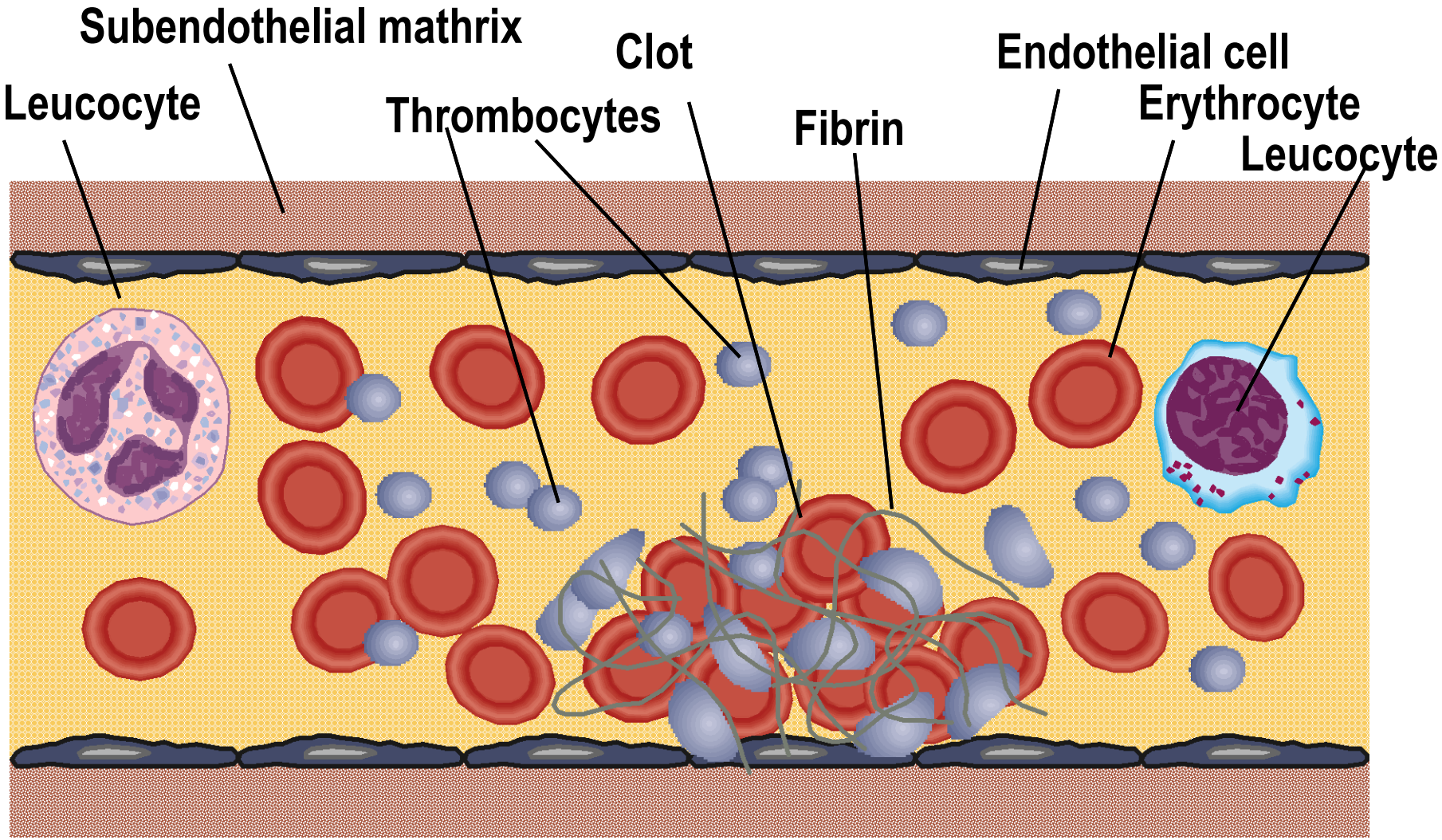
Fibrinolytic system

- **Plasminogen**
- **F XII (F. Hagemann, of contact)**
  (intrinsec pathway of Plasminogen activation)
- **Tissular (endothelial) activator of Plasminogen**
  (extrinsec pathway of plasminogen activation)

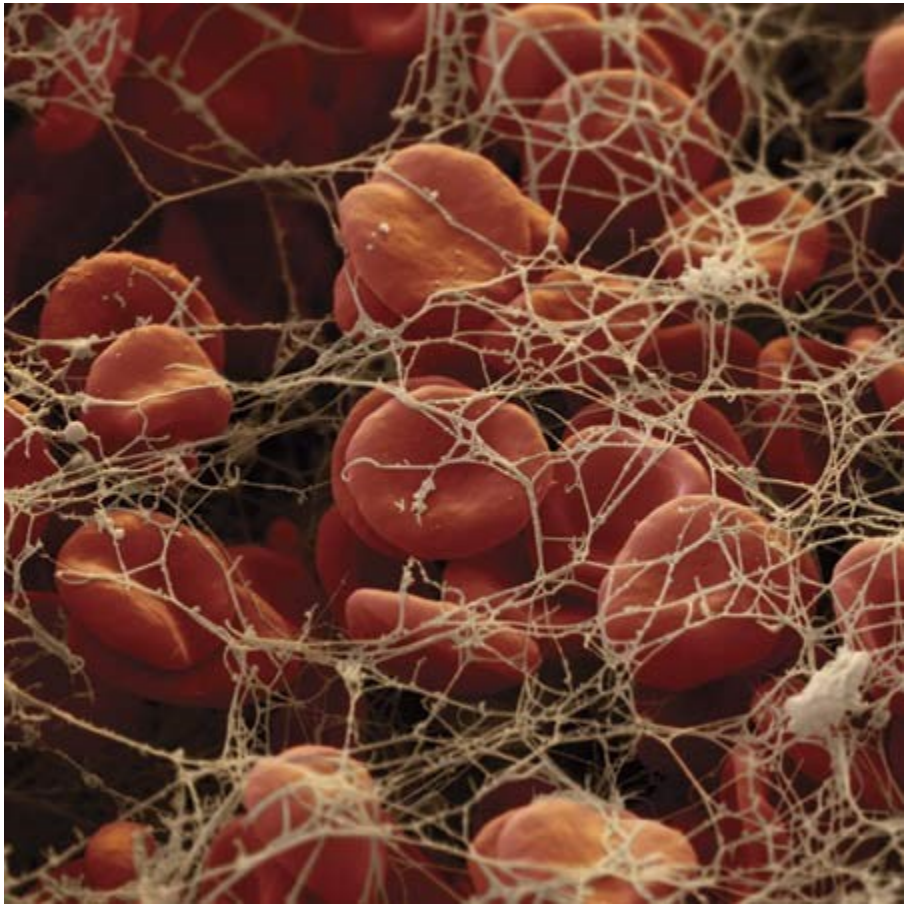
Physiologic anticoagulants

- **Heparin**
- **Antitrombin III**
- **Protein C**
- **Protein S**
- **Thrombomodulin**
- **Antithromboplastin**
- **α_2-antitripsin**

Hemostasis


Subendothelial mathrix
Clot
Endothelial cell
Leucocyte
Thrombocytes
Fibrin
Erythrocyte
Leucocyte

Erytrocytary red clot



Hemorrhagic diatheses

Non homogeneous group of pathologies
characterized clinically
by increased tendency to bleeding

Classification of HD

- **HD as a result of**

  primary vasculo-thrombocytary hemostasis disorder

- **HD as a result of secondary hemostasis disorder (coagulopathies)**

- **Mixt HD as a result of primary and secondary hemostais disorder**

HD as a result of primary vasculo-thrombocytary hemostasis disorders

- **Thrombocytopenias**
  - **Congenital (Sd. Casabach-Merritt)**
  - **Acquired (hetero/izo/auto-immune)**
- **Thrombocytopathies:**
  - **Congenital (TAR, Glanzman, Bernard-Soulier)**
  - **Acquired (cirrhosis, scorbutus, medicamentous)**
- **Vasopathies:**
  - **Disease Rendu-Osler-Weber**
  - **Schönlein-Henoch purpura**

HD as a rezult of secondary hemostasis disorder(coagulopathies)

- **Hypo/a-fibrinogenemia**
- **Hypoprothrombinemia**
- **Hypoproaccelerinemia**
- **Hypoproconvertinemia**
- **Hemophilia A**
- **Hemophilia B (Christmas)**
- **Deficit of F X (Stuart-Prower)**
- **Hemophilia C (Rosenthal)**
- **Hagemann disease (F XII)**
- **Deficit of F XIII (fibrinstabilizer)**

Mixt HD

- **Von Willebrand disease**
- **Disseminated intravascular coagulation (DIC) Syndrome**

Diagnosis of HD

- **Clinical data**
- **Laboratory data**

Clinical diagnosis of HD

? ? ?

- **Is the hemorrage a disorder of hemostasis**
  or is a manifestation of
  local tissue modifications ?

- **If there is an affection of hemostasis,**
  which is its character:
  congenital or acquired?

- **Appreciation of clinical manifestations with determining of bleeding type**

Types of bleeding

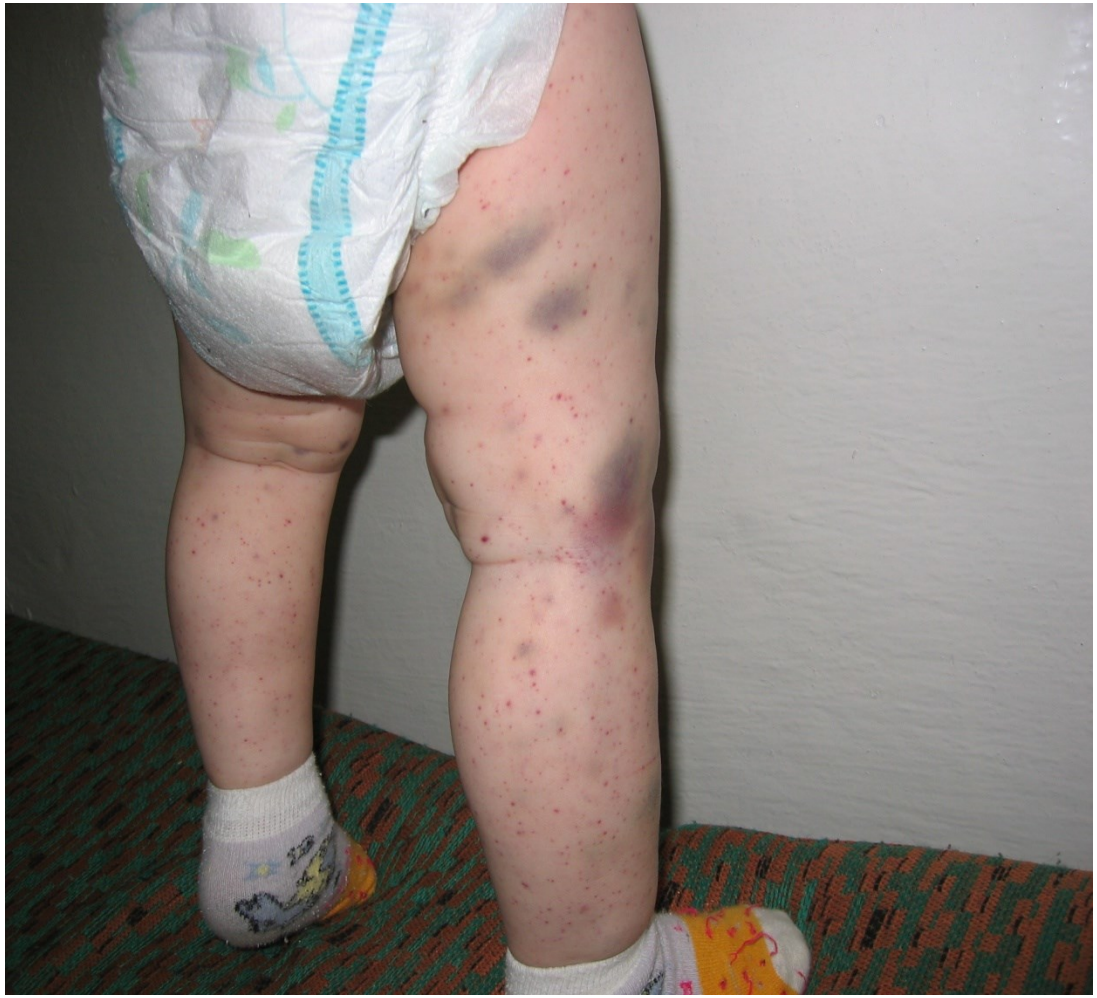
- **Petechial-macular**
- **Hematoma**
- **Mixt**
- **Vascular – purpural**
- **Angiomatous**

Petechial-macular

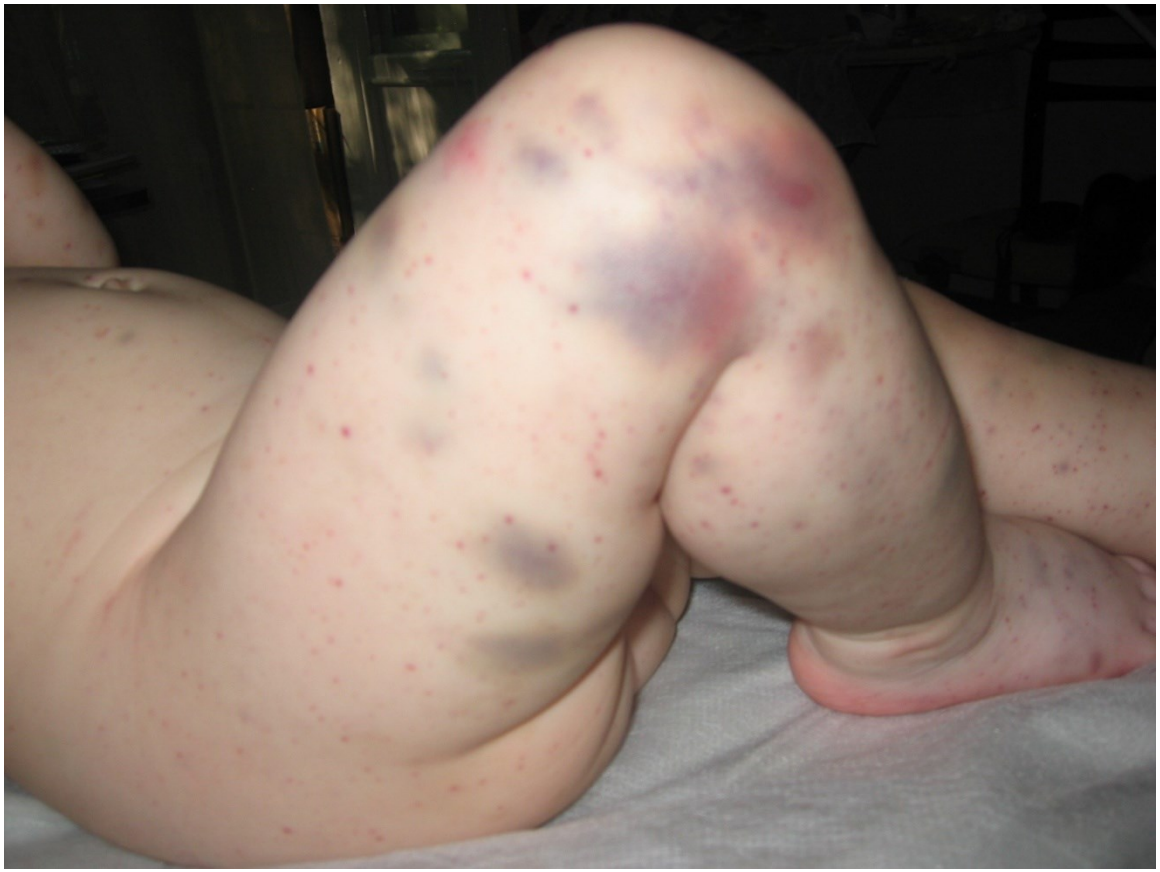
- **Hemorrhagic elements by small calibre (petechiae)**
- **Nonuniform hemorrhages, by different colour (echimoses)**
- **Indolor, not tensioned and not stratificate the tissues**
- **Often are associated with epistaxis, gingivorragies,metrorragies**
- **More seldom- with hemorrages in sclera, meninx and in stomach**
- **Appear easily after microtraumatism of capillaries**

- **Disorder of primary hemostasis (vasopathies, thrombocytopathies/-penias)**

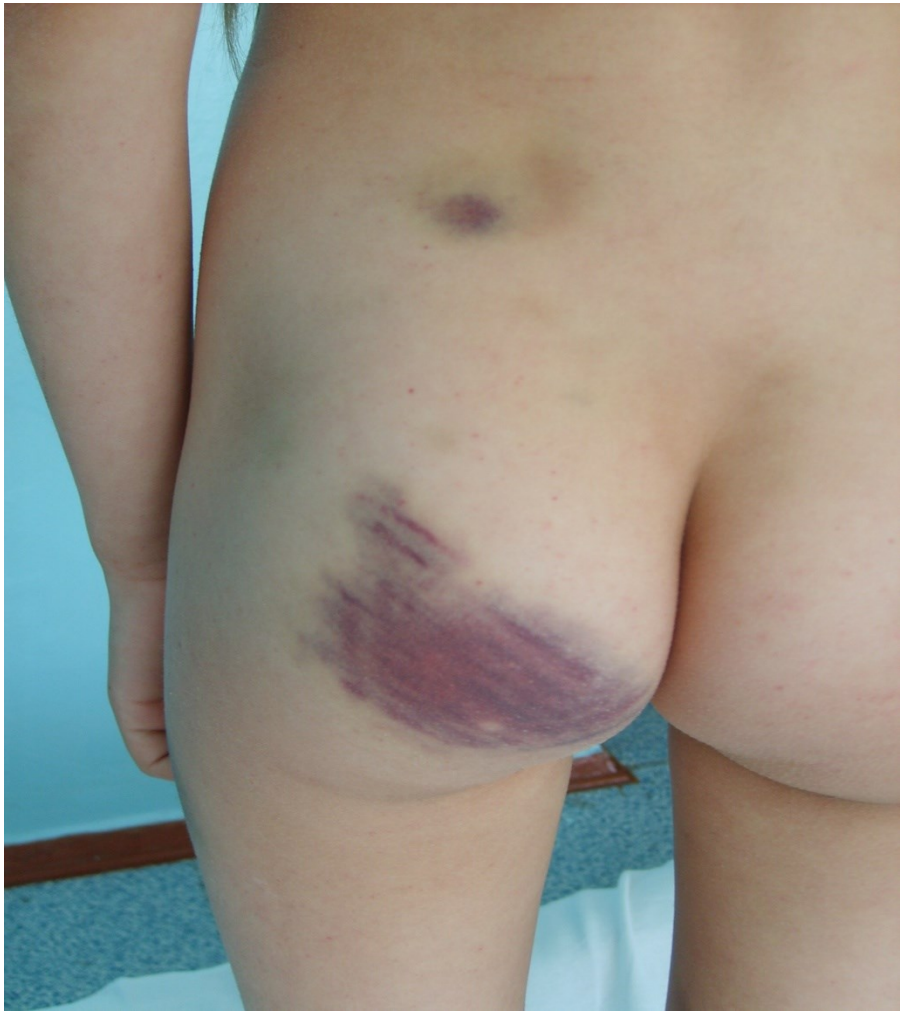
Petechial-macular



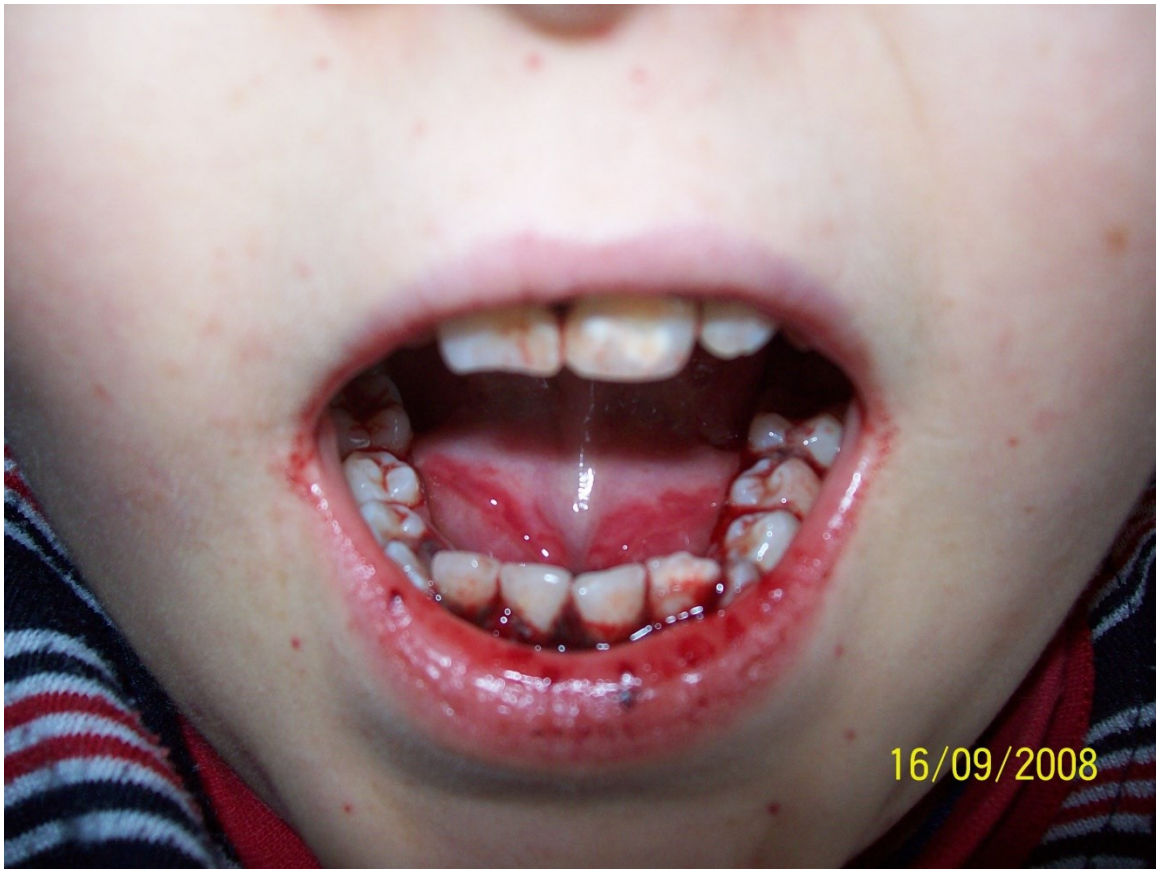
Petechial-macular



Petechial-macular



Petechial-macular



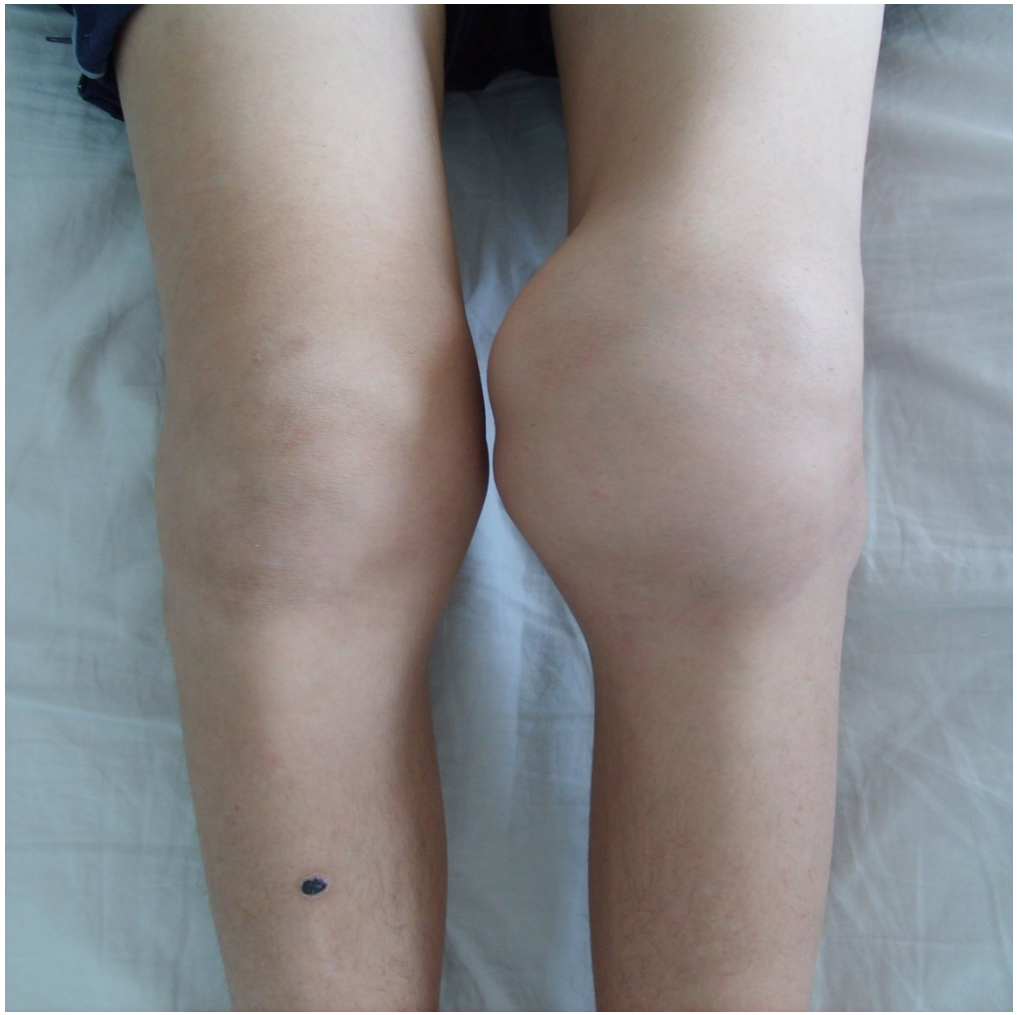
Hematoma

The following hemorrhages prevail:

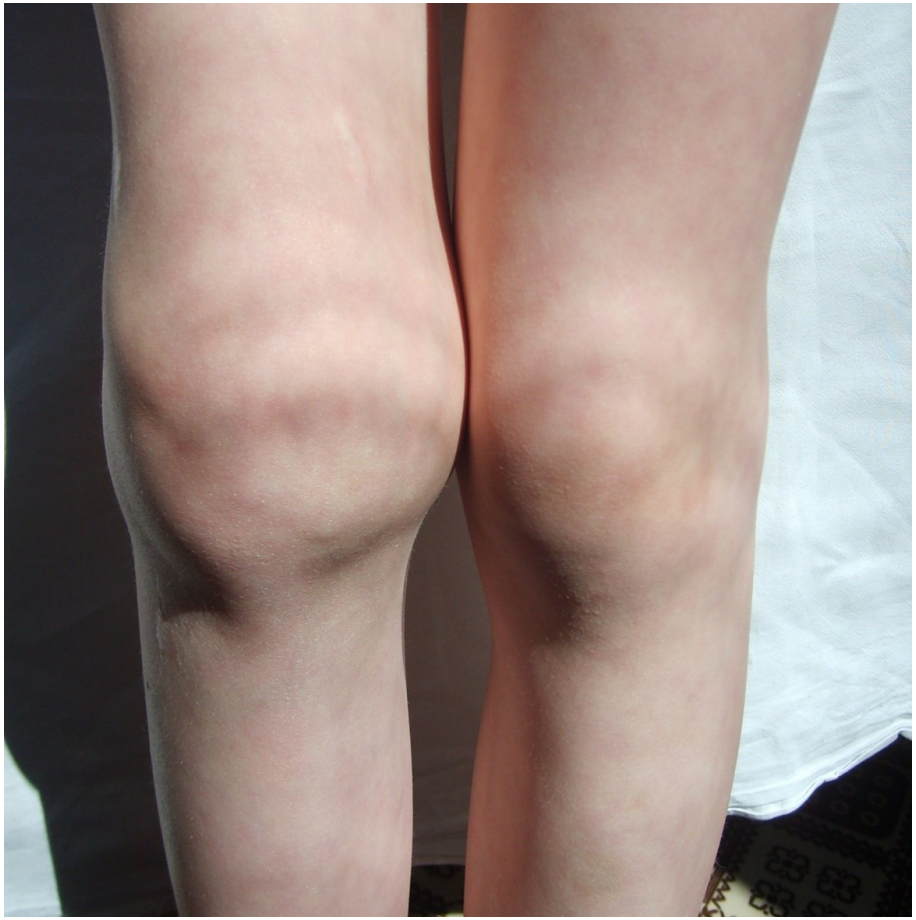
- **Massive, profound, tensioned and very painful**
- **In articulations, muscles, under aponeuroses,**
  in adipose subcutaneous tissue
- **extraperitoneal, in peritoneum**
  and intestinal submucosa
- **hematomas are easily forming in the place of injections**
- **They appear during a few hours after surgical intervention or after trauma.**

- **Isolated hemorrhage by hematoma type are characteristic for hemophilia A and B.**

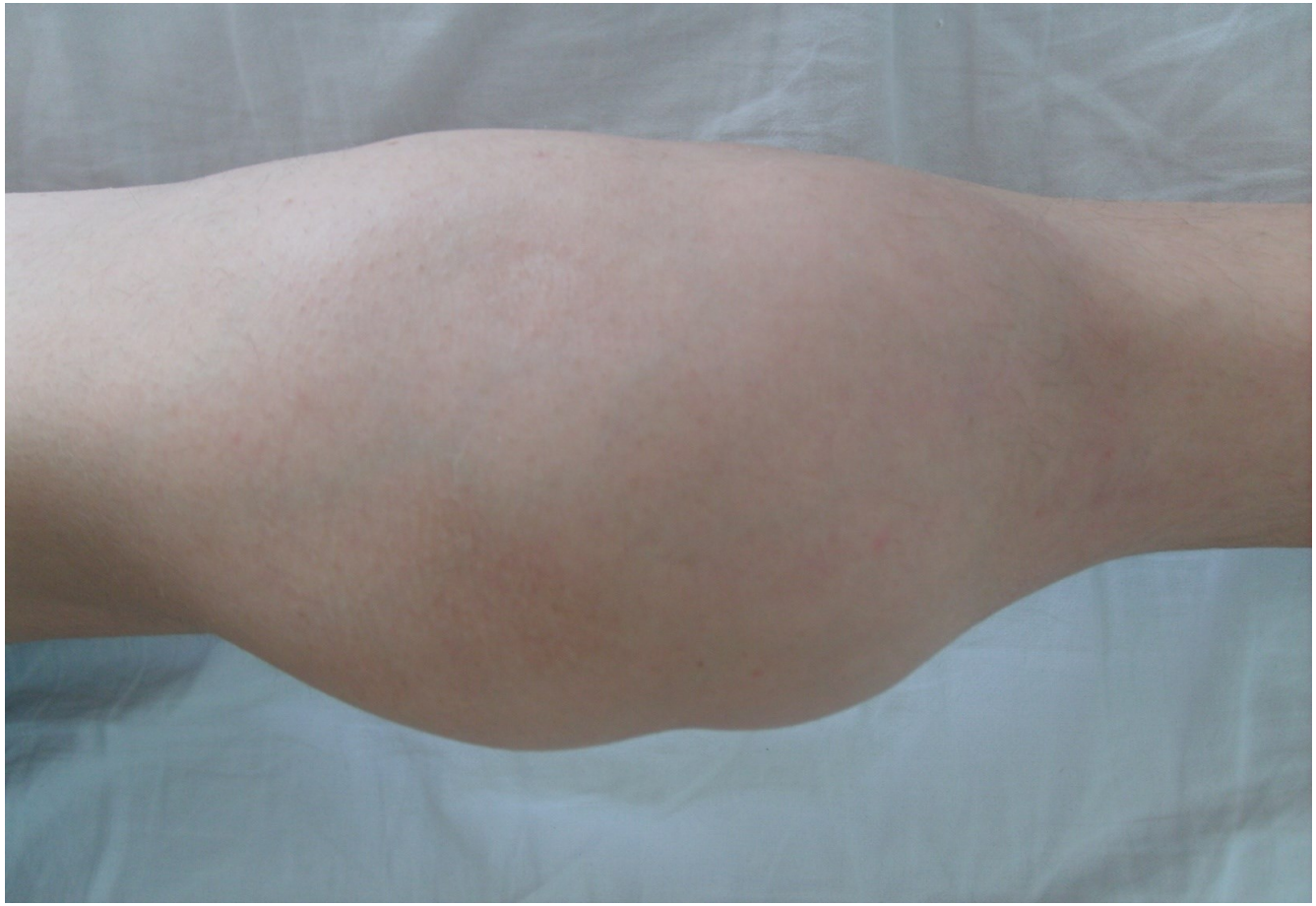
Hematoma



Hematoma



Hematoma



Mixt type (petechial-macular-hematoma)

It is delimited by hematoma type by:

- Easier and very rare affection of articulations,
- Predominance of hematomas
  in subcutaneous tissue,
  extraperitoneal and in internal
  organs.

Mixt type (petechial-macular-hematoma)

It differs from petechial-macular type by:

- Massivity of cutaneous elements
- Induration of skin in the places of hemorrhage

Mixt type (petechial-macular-hematoma)

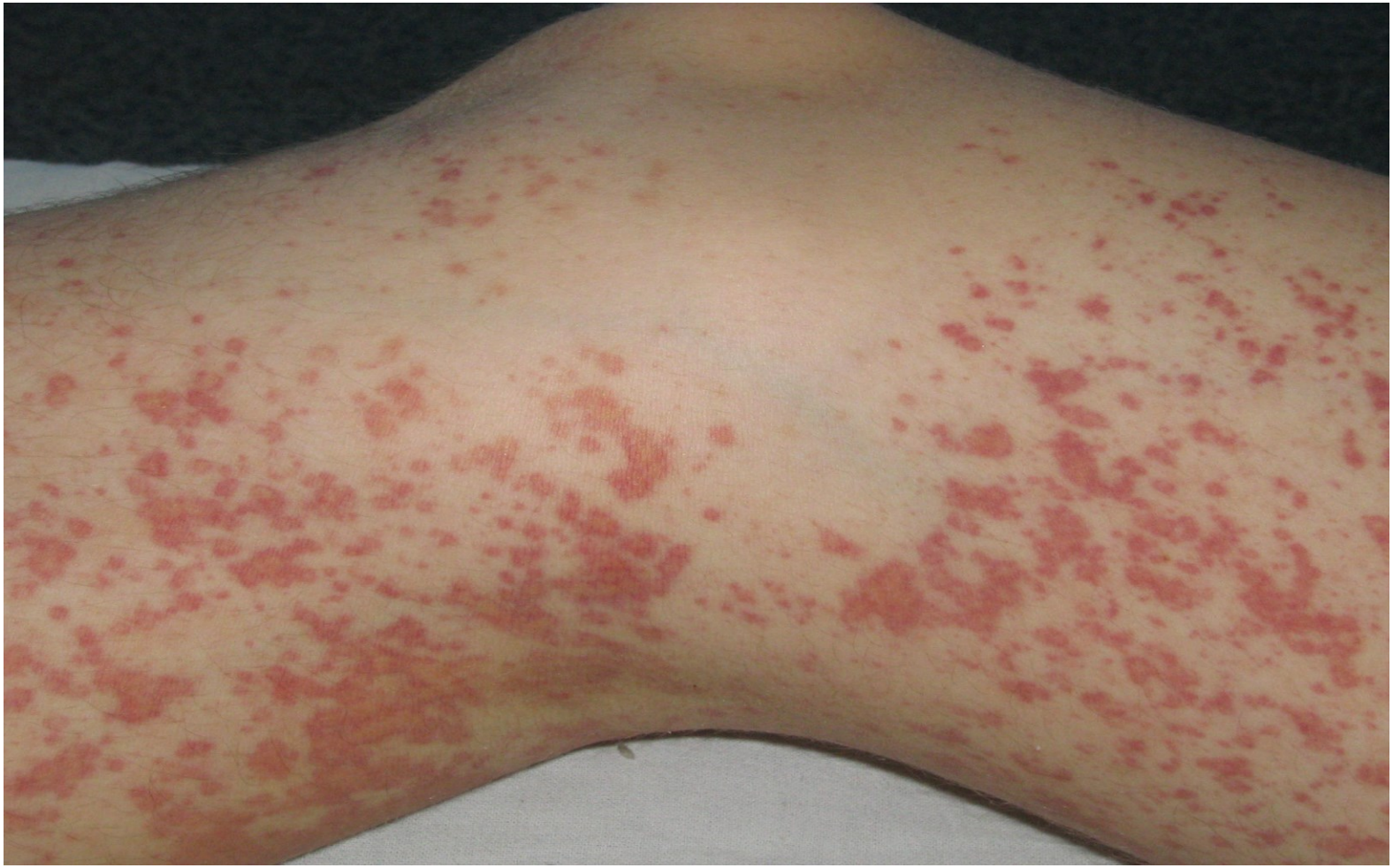
- The bleeding begins by
  petechiae, echimoses and epistaxis,
  which gradually are transforming in hematomas.

- Characteristic for
  von Willebrand disease, DIC syndrome,
  profound deficit of F VII and XIII

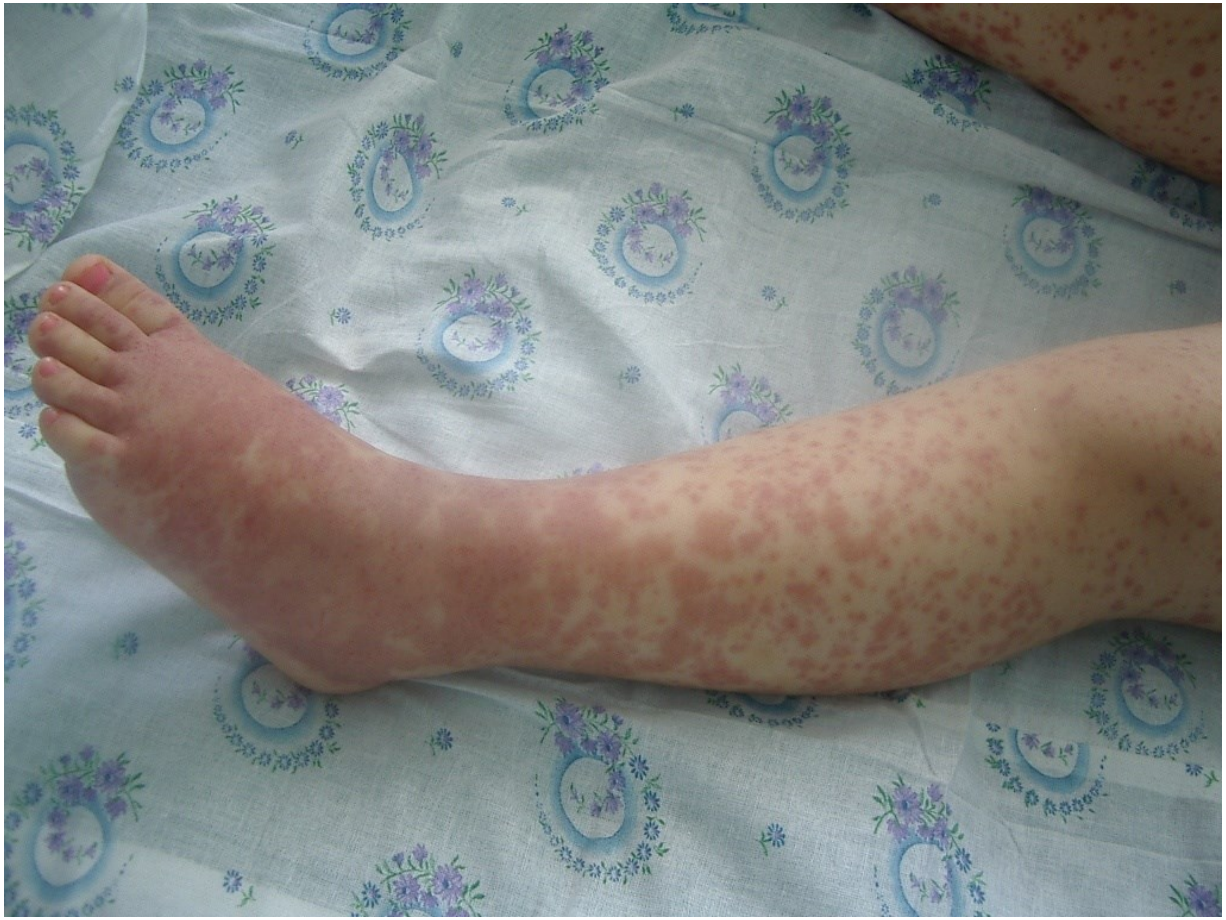
Vascular – purpural

- They are determined by inflammatory modifications in small calibre vessels and perivascular tissues
- They are followed by local exudative-inflammatory modifications
- Eruptions throw into relief over skin level
- They are hard, form infiltrative pigmented border
- Sometimes they submit to necrosis and form crusts
- They regress with long-time keeping of pigmentation
- They are observed in Schönlein-Henoch purpura, hemorrhagic fevers

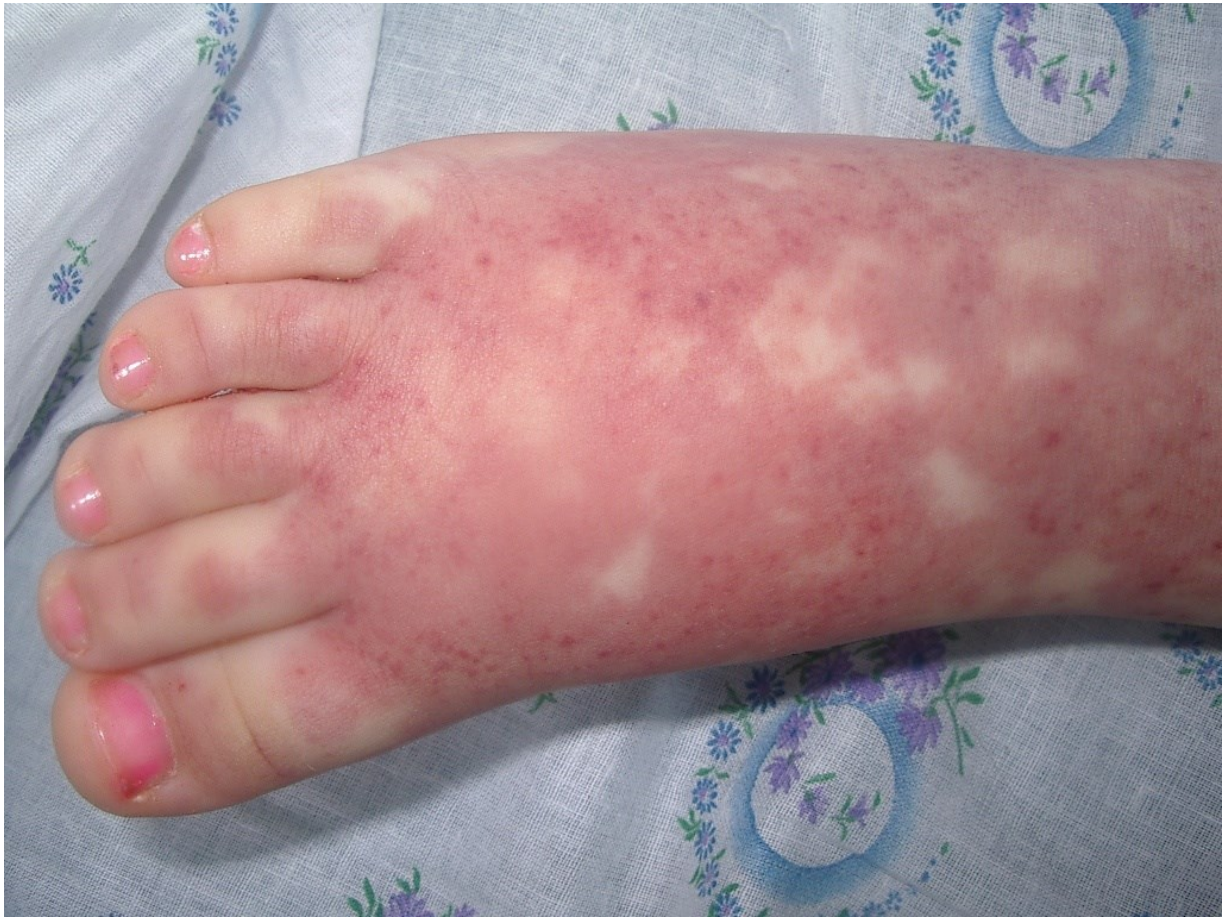
Vascular – purpural



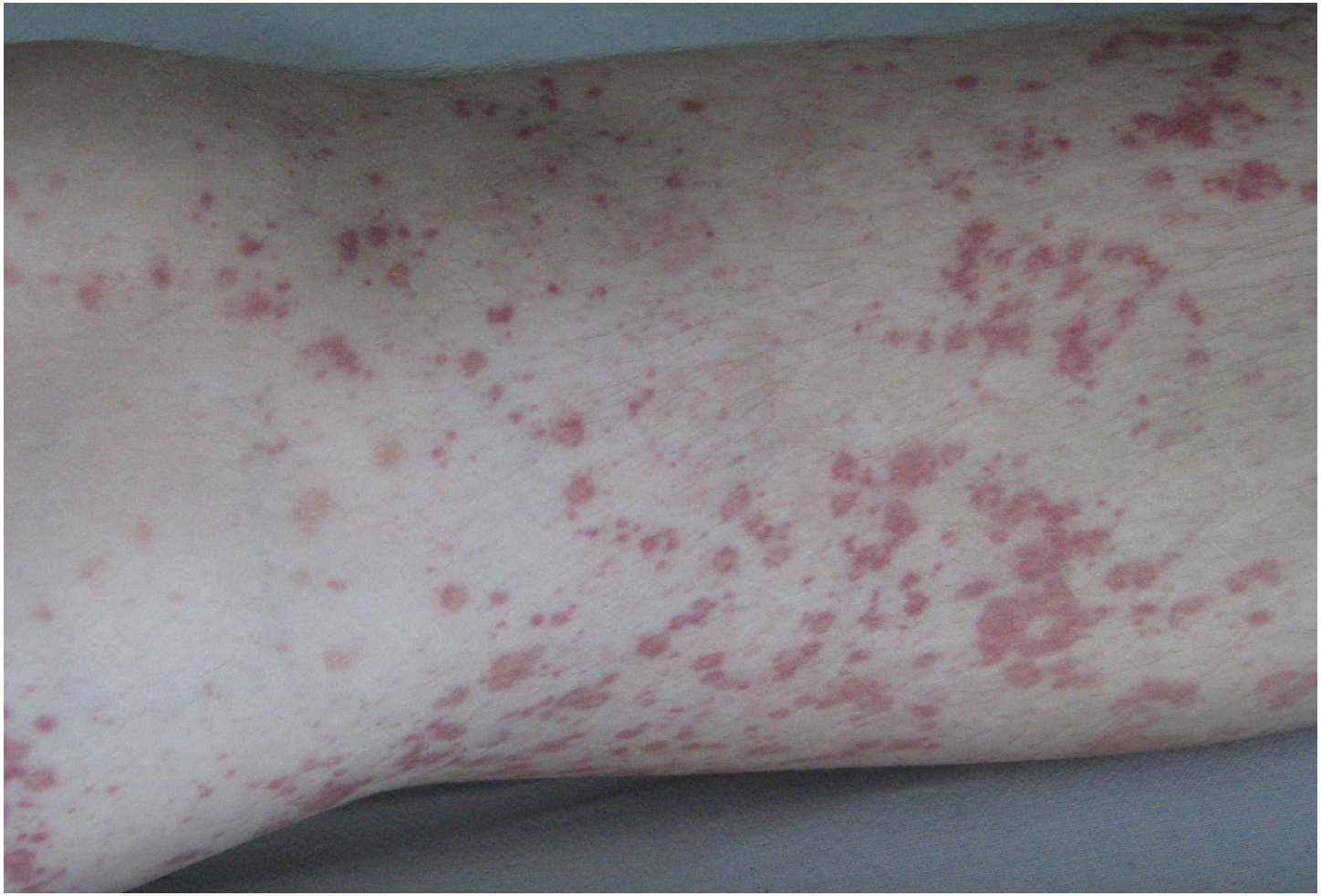
Vascular – purpural



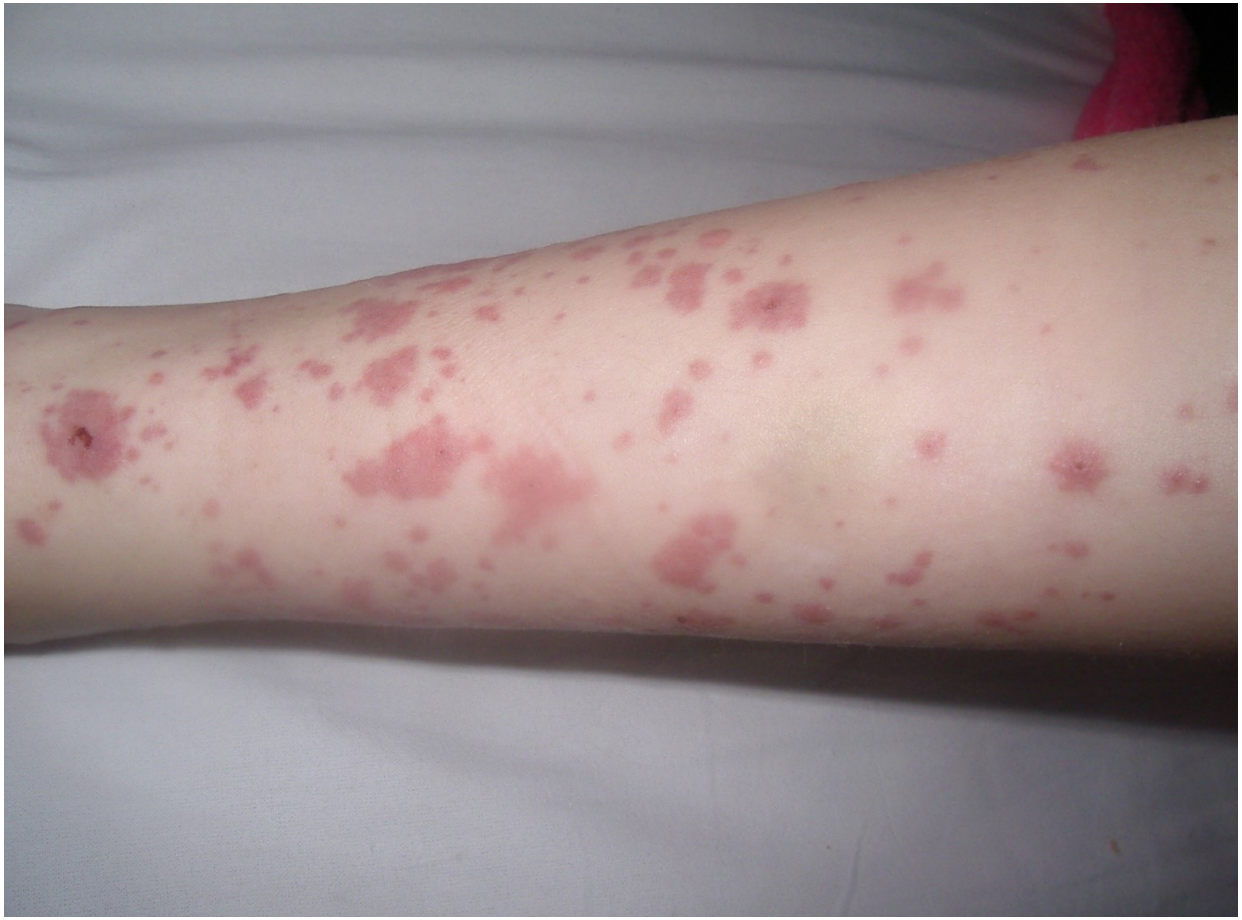
Vascular – purpural



Vascular – purpural



Vascular – purpural



Angiomatous

- **Repeated hemorrhages from dysplasiated vessels with certain localization**
- **Without hemorrhages in skin, adipose tissue**

  or in other tissues
- **The most frequent and more severe are:**
- **Nasal hemorrhages (epistaxis)**
- **Rarer-hemorrhages from gastric, intestinal, renal and pulmonary teleangiectasies.**
- **Laboratory tests don’t find disorders of humoral hemostasis system.**
- **In diseases Rendu-Osler-Weber, Louis-Barr,**
- **In hepatic cirrhosis (secondary)**

Laboratory diagnosis of Hemorrhagic diatheses

- **Methods of primary hemostasis appreciation**
- **Methods of secondary hemostasis appreciation**
- **Appreciation of fibrinolytic activity**
- **Appreciation of physiologic anticoagulants**

Primary hemostasis appreciation tests:

Vessels:

- Fragility and capillary resistance

Thrombocytes:

- Number of thrombocytes
- Morphology of thrombocytes
- Bleeding time(Duke, Ivy, Shitikov)
- Clot retraction reaction
- Appreciation of adhesion and aggregation

Fragility and capillary resistance

- **Compression test (with tonometer cuff)**
- **Pinch test**

Rumpel-Leede test

Is performing by hand compression with tonometer cuff.

The applied pressure is equal to medium arterial pressure value.

The application duration constitutes 5 minutes.

After that we number the petechiae appeared on the arm in the area of circle with the diameter of 20 mm.

Normal value: under 10 petechiae,

10-20 petechiae–Rumpel-Leede test is slightly positive (+),

20-30 petechiae – positive test (+ +),

More than 30 petechiae –intense positive test(+ + +).

The test is positive in hereditary vascular disorders, in thrombocytopenies, thrombocytopathies, in hemorrhagic vasculitis.

Pinch test

- **At the level of medium third of clavicle the pinch of tegument an adipose subcutaneous tissue is applied. The result is reading afte 24 hours.**
- **Normally the eruptions are not present or 3 – 5 eruptive element are present.**
- **The test is positive in vasopathies thrombocytopathies, thrombocytopenies**

The number and morphology of thrombocytes

- **The count of thrombocytes**

(Feisely's technique), is more difficult in comparison with another sanguin elements due to less dimensions of thrombocytes and tendency to aggregation in vitro.

Normal values: 150.000-400.000 / mm^3.

The count of thrombocytes decreases in thrombocytopenies,

DICS, HUS, autoimmune diseases(SLE),

aplastic anemias, leucemias, metaplastic anemias.

- **Morphology of thrombocytes**
- **Microcytosis in Wiskott-Aldrich syndrome**
- **Gigantic thrombocytes in Bernard-Soulier syndrome**

Duke's bleeding time

- **The ear lobe is pricked with an vaccinostyle.**

  The chronometer is starting at the appearance of first blood drop.

  At every 30 seconds the blood drops are collected on the filter paper.

  The chronometer is stopping when the paper is not more spotting.

- **Normal value: 3 minutes,**

  3-5 minutes – slightly prolonged,

  more than 5 minutes – pathologic.

- **BT is prolonged in vasculopathies, thrombocytopathies, thrombocytopenias, von Willebrand disease,**

  very rare in severe coagulopathies.

Appreciation of clot retraction

- **It characterizes the thrombocytary function in the last phase of coagulation and is directly dependent from the number of thrombocytes.**
- **5 mL of venous blood is collected in conic graduated test tube (without stabilizer), a glass stick is placed on the tube center and the tube is incubated at 37 C. The tube periodically is inclined in opposite parts until the clot appearance. After one hour the glass stick is extracted and the volume of remained serum is appreciated.**
- **Normal value: 48 – 62%**

- **Decreased values: thrombocytopenias,**

  false decreased - in polyglobulia, erythremia
- **False increased values - in anemia, hypofibrinogenemia**

Aggregation function examination

- **Diagnosis of hereditary and acquired thrombocytopaties:**
- **Diagnosis of hypoaggregant type hereditary thrombocytopathies (Bernard-Soulier, Glantzmann's thrombastenia)**
- **Diagnosis of hypoaggregant type acquired thrombocytopathies (uremia, cirrhosis, medicaments, toxins)**
- **Diagnosis of hyperaggregant type acquired thrombocytopathies (diabetus mellitus, hyperlipoproteinemias, paraproteinemias)**

- **Antiaggregant therapy control**

Inductors of thrombocytary aggregation

- **ADP**
- **Collagen**
- **Ristomycin**
- Adrenalin
- Serotonin
- Thromboxan A2

Requests for thrombocytes aggregation investigation

- **The rich in thrombocytes plasma (RTP) is used for investigation**
- **Thrombocytes number in RTP**

  200 – 250 thousands/mL
- **Using of different inductors**
- **Using of inductors in different concentrations**
- **Immediate procession of colected probe**
- **Excluding of medicaments that can**

  influence aggregation

Obtaining of probes

- **Collection of venous blood using the needle without syringe**
- **(The ratio blood:citrate – 9:1)**
- **Using of plastic test tubes at all stages of investigations**
- **Obtaining and separation of rich in thrombocytes plasma (centrifugation 1000 – 1500 tur/min during 5 – 7 min)**
- **Obtaining of poor in thrombocytes plasma (centrifugation of remained blood 3000 tur/min during 15 min)**

Parameters of aggregation

- **Degree of aggregation–**

  Maximal level of aggregation
- **Speed of aggregation–**

  Increasing of aggregation degree per minute
- **Aggregation time–**

  time of maximal aggregation
- **Duration of „lag”-phase –**

  at aggregation with collagen

Hypoaggregation

- **Diminishing of aggregation degree**
- **Diminishing of aggregation speed**
- **Presence of desaggregation**
- **Absence of second aggregation phase**
- **Increasing of „lag”-phase**

Hyperaggregation

- **Increasing of aggregation degree**
- **Increasing of aggregation speed**
- **Presence of monophasic aggregation curve (merging of I and II aggregation phase)**

Factors that can influence the aggregation of thrombocytes

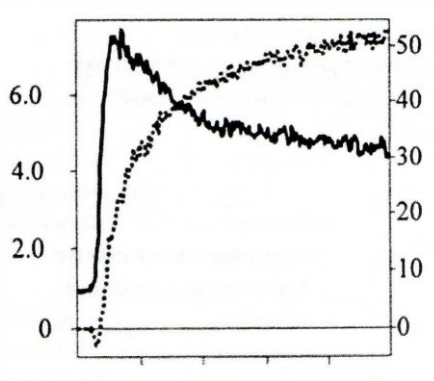
- **Increase:**
  - **Oral contraceptives;**
  - **Smoking**
- **Decrease:**
  - **Antiaggregants (aspirin, dipiridamol, ticlid)**
  - **Glucocorticosteroids**
  - **Adrenoblockers**
  - **Blockers of Calcium channels**
  - **Heparin, Fraxiparin**
  - **Vitamins C and E**
  - **Antibiotics (penicillin, carbenicillin)**
  - **Diet (fish diet during 2-3 weeks)**

Aggregation with ADP

- Characteristic modification of thrombocytes form.

- Irreversible aggregation.
- Aggregation 52%.
- Dimension of aggregates 6,9 UI.

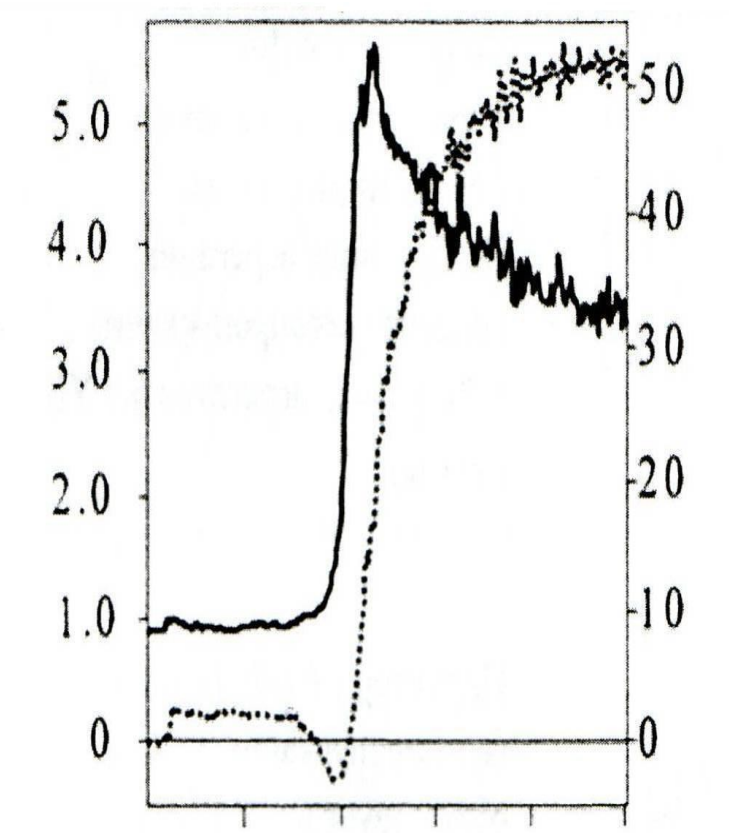
- Norma: 50 – 80%



Aggregation with collagen

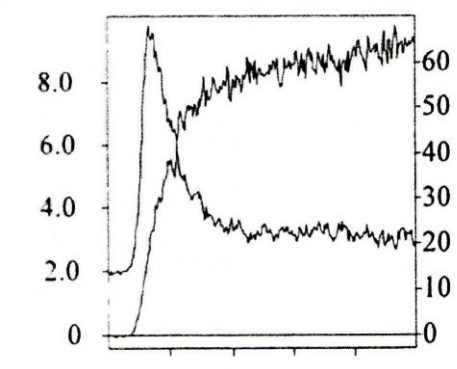
- Lag-phase characteristic in the first minute.
- Aggregation 53%.
- Dimension of aggregates 5,7 UI.

- Norma:50 – 70%



Aggregation with Ristomycin

- Aggregation 68%.
- Dimension of aggregates 8,9 UI.
- Norma: 50 – 80%



Differential diagnosis of hemorragic diatheses

	ADP		Collagen	Ristomycin
	I phase	II phase		
von Willebrand disease	**N**	**N**	**N**	↓ ↓ ↓ / ↑
von Willebrand syndrome	**N**	**N**	**N**	↑ **1,5 – 2 times**
Bernard-Soulier syndr.	**N**	**N**	**N**	↓ ↓
Glantzman's thrombastenia	↓	↓	↓	**N**
Syndrome of grey thrombocytes	↓	↓ / ↓↓	↓	**N**
Deficit of granules	↓	**Absent**	↓	**N**
Defect of collagen recptor	**N**	**N**	↓↓↓	**N**
Aspirin overdosing	↓	↓	↓	**N**

Tests of secondary hemostasis appreciation:

- **Global methods**
- **Analytic methods**
- **Quantitative methods**

Global methods

- **Coagulation time by Lee-White method**

  The vein is punctured and 2 ml of blood are collected. It is distributed in 2 test tubes in equal quantities. They are placed in water bath at 37º C. The chronometer is started when the blood is getting in syringue. At each minute the test glass is readed by inclination of 45º.

  CT is determined in the moment when the test tube can be completely overturned. In this moment the reading of test tube begins at each 2 minute. CT is the time passed from the chronometer starting until appearance of coagulation in the 2-nd test tube.

  Normal values: 6-12 minutes.

- **Howell time**

  It represents the time of oxalate or citrate plasma coagulation after recalcification.

  Besides plasmatic factors, HT appreciates also the thrombocytary function(F3P).

  Normal values: 1'10'' – 2'10''.

  There is the main test used for heparin therapy monitoring.

Analytic methods

- **Intrinsic pathway**
  - Partial time of thromboplastin
  - Partial time of activated thromboplastin

- **Extrinsic pathway**
  - Quick prothrombin time (PT)

- **Common pathway**
  - Thrombin time

Intrinsic pathway

- **Partial thromboplastin time (cephalin)**

  It allows to appreciate the thromboplastin forming on endogenous pathway (intrinsic).

  The technique is similar to that of HT but the supplement of cephaline ensures the independence from F3P.

- **Normal values: 70-110 seconds.**
- **It is changed in the deficit of factors**

  XII, XI, X, IX, VIII, I and severe deficit of factors V and II.

- **Partial time of Activated Thromboplastin**

  (cephalin-kaolin).

  The adding of kaolin in PTT test excludes the influence of factors XII and XI on coagulation, therefore PTAT being a valuable screening test of antihemophilic factors.

- **Normal values: 35-50 seconds.**
- **It is changed in the deficit of factors X, IX, VIII, I**

  and severe deficit of factors V and II.

Extrinsic pathway

- **Quick's prothrombin time (Quick PT)**

  It explores the factors of protrombinic complex

  (VII, X, V, II) and fibrinogen.

  In the presence of tissular tromboplastin and calcium chloride, the normal plasma is coagulating in very short time (10 seconds), rounding the first phase of coagulation (intrinsec).

- **Normal values: 13-15 seconds**

- **It is modified in hepatic affections and vitamin K insufficiency.**

Common pathway

- **Thrombin time**

  The adding of thrombin in plasma probe allows to appreciate the fibrin forming, without the first two phases of coagulation.

- **Normal values: 20-30 seconds**
- **Prolonged time in hypofibrinogenemias (< 1,5 g/l)**

  or in presence of some circulant anticoagulant.

  Hyperfibrinogenemia over 4,0 g/L can take moderate prolonging of TT.

- **Fibrinogen quantity determining**
- **Normal values: 2-4 g/l.**

Quantitative methods

- Fibrinogen
- Prothrombin
- Calcium in blood serum
- **F VIII**
- **F IX**
- **F XIII**

- **von Willebrand:RCoF**

Content / Activity of coagulation factors

Factor	Naming	Content
I	**Fibrinogen**	2 – 4 g/l
II	**Prothrombin**	60 – 150 %
III	**Tissue thromboplastin**	
IV	**Calcium ions**	1,9 – 2,7 mmol/l
V	**Proaccelerin**	60 – 150 %
VII	**Proconvertin**	65 – 135 %
VIII	**AHF A**	60 – 145 %
IX	**AHF B, f. Christmas**	60 – 140 %
X	**F Stuart-Prawuer**	80 – 120 %
XI	**AHF C**	65 – 135 %
XII	**F Hagemann**	65 – 150 %
XIII	**Fibrinstabilizer factor**	100 %

Laboratory differentiation of coagulopathies

Pathology	BT	PTAT	PT	T T
Hemophilia A	**N**	↑	**N**	**N**
Hemophilia B	**N**	↑	**N**	**N**
Hemophilia C	**N**	↑	**N**	**N**
vWillebrand disease	↑	**N or ↑**	**N**	**N**
Owren disease (F V)	**N**	↑	↑	**N**
Alexander dis. (F VII)	**N**	**N**	↑	**N**
Stuart-Prauer disease (F X)	**N**	↑	↑	**N**
Deficit of F XII	**N**	↑	**N**	**N**

Crossed probes of correction

For this test are used:

- **Usual plasma from healthy person**

  Contains F: I, II, V, VII, VIII, IX, X, XI, XII, XIII

- **Barium sulphate adsorbed plasma**

  Contains F: I, V, VIII, XI, XII, XIII

- **serum from healthy person**

  Contains F: VII, IX, X, XI, XII

Crossed probes of correction

Deficit factor	PTT	PTAT	TT	Normal plasma	Adsorbed plasma	Serum
II	↑	↑	↑	Corrects	Corrects	**Doesn't correct**
V	↑	↑	N	Corrects	Corrects	**Doesn't correct**
VII	↑	N	N	Corrects	**Doesn't correct**	Corrects
VIII	N	↑	N	Corrects	Corrects	**Doesn't correct**
IX	N	↑	N	Corrects	**Doesn't correct**	Corrects
X	↑	↑	N	Corrects	**Doesn't correct**	Corrects
XI	N	↑	N	Corrects	Corrects	Corrects
XII	N	↑	N	Corrects	Corrects	Corrects

Appreciation of fibrinolysis

- **Time of euglobinic clot lysis**

  Normal values: males 150 ± 30 seconds,

  females 180 ± 30 seconds.

- **Test for evidence of**

  Fibrin Degradation Produces (FDP).

  Normal values: <4 µg/mL

- **Test of fibrin monomers evidence(FMT).**

Appreciation of fibrinolysis

- **Time of euglobinic clot lysis**
- **FDP and FMT**

  increase in:
- **DICS**
- **Thrombembols**

Contain / activity of principal anticoagulant factors

Factor	Contain or activity in plasma
Antithrombin III	Activity 80 – 120 %
Heparin	0,24 – 0,6 UI/ L
Protein C	Contain in plasma 70 – 130 %
Protein S	Contain in plasma 60 – 140 %

Contain / activity of principal anticoagulant factors

- **Antithrombin III**
- **protein C**
- **protein S**

are decreased in :

- **Thrombophilias**
- **DIC syndrome**

Principles of primary hemostasis disorders treatment

- **Corticotherapy**
- **Vasoprotectors**
- **Immunodepressants**
- **Splenectomy**

Principles of secondary hemostasis disorders treatment

- **Substitution therapy with:**
- **Fresh frozen plasma**
- **Cryoprecipitate**
- **Purifyed coagulation factors precipitates**

THANK YOU
FOR ATTENTION