Disorders of Hemostasis

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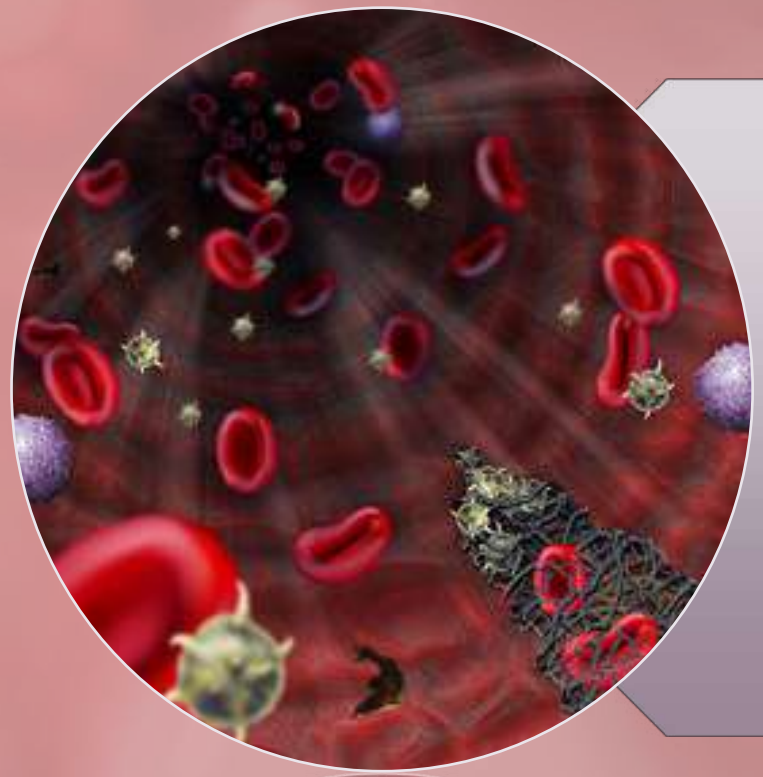
Objectives

1. Hemopoiesis.
2. Anemia, Types and Related Disorders.
3. Granulopoiesis and White Blood Cell Disorders.
4. Hematological Malignancies.
5. **Hemostasis.**
6. Transfusion Medicine.



HEMOSTASIS

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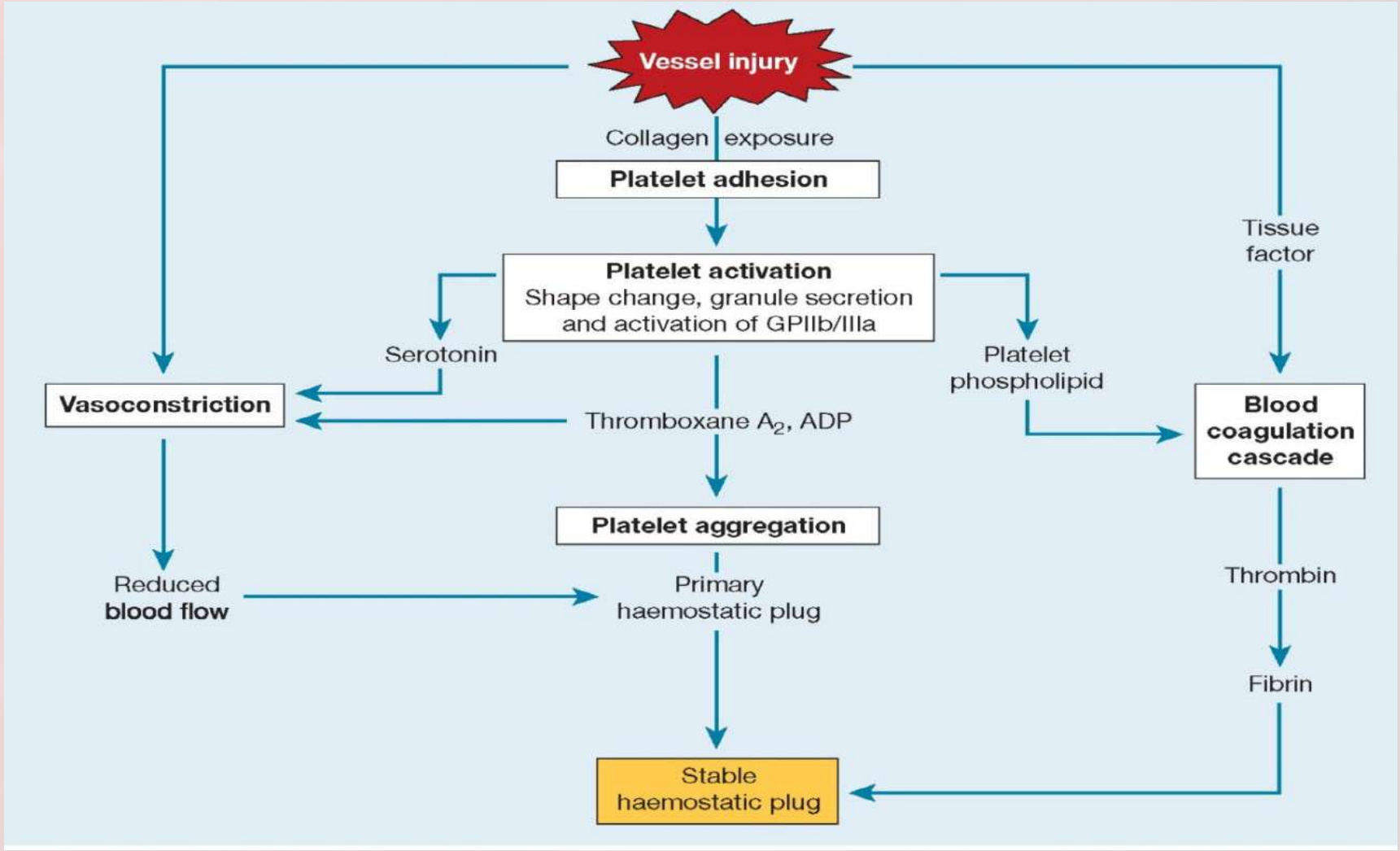
Process of response to vascular damage, performed by interaction of blood vessel wall, platelets and coagulation factors



1- Blood vessels;

Vasoconstriction; immediate for the injured with a rapid reflex of the adjacent vessels, leading to slowing of the blood flow to the injured area.

2- Platelets;

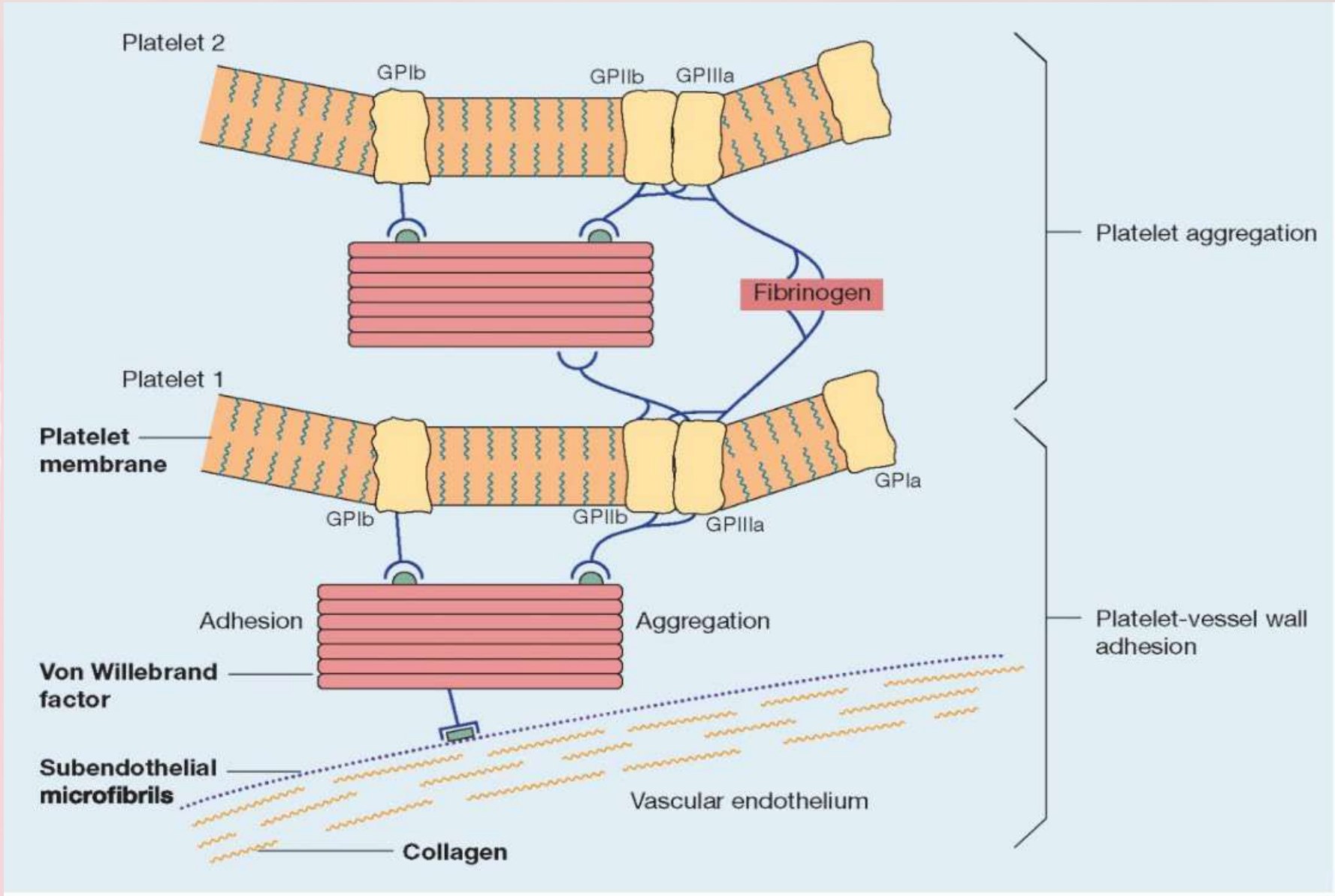
Produced from the BM megakaryocytes cytoplasmic fragmentation, with a main function of plug formation during hemostasis

It acts by 3 mechanisms;

1. Adhesion
2. Aggregation
3. Activation

Presence of von Willebrand factor (VWF) is the important mediator for 1&2 mechanisms, which also interacts with factor VIII. Platelet also play an important role in coagulation cascade by its storage granules.

- The net effect of vasodilatation and inhibition of platelet function is to promote blood fluidity.
- The net effect of vasoconstriction and platelet activation is to promote thrombosis.
- Thus, blood fluidity and hemostasis is regulated by the balance of antithrombotic / prothrombotic and vasodilatory / vasoconstrictor properties of endothelial cells.

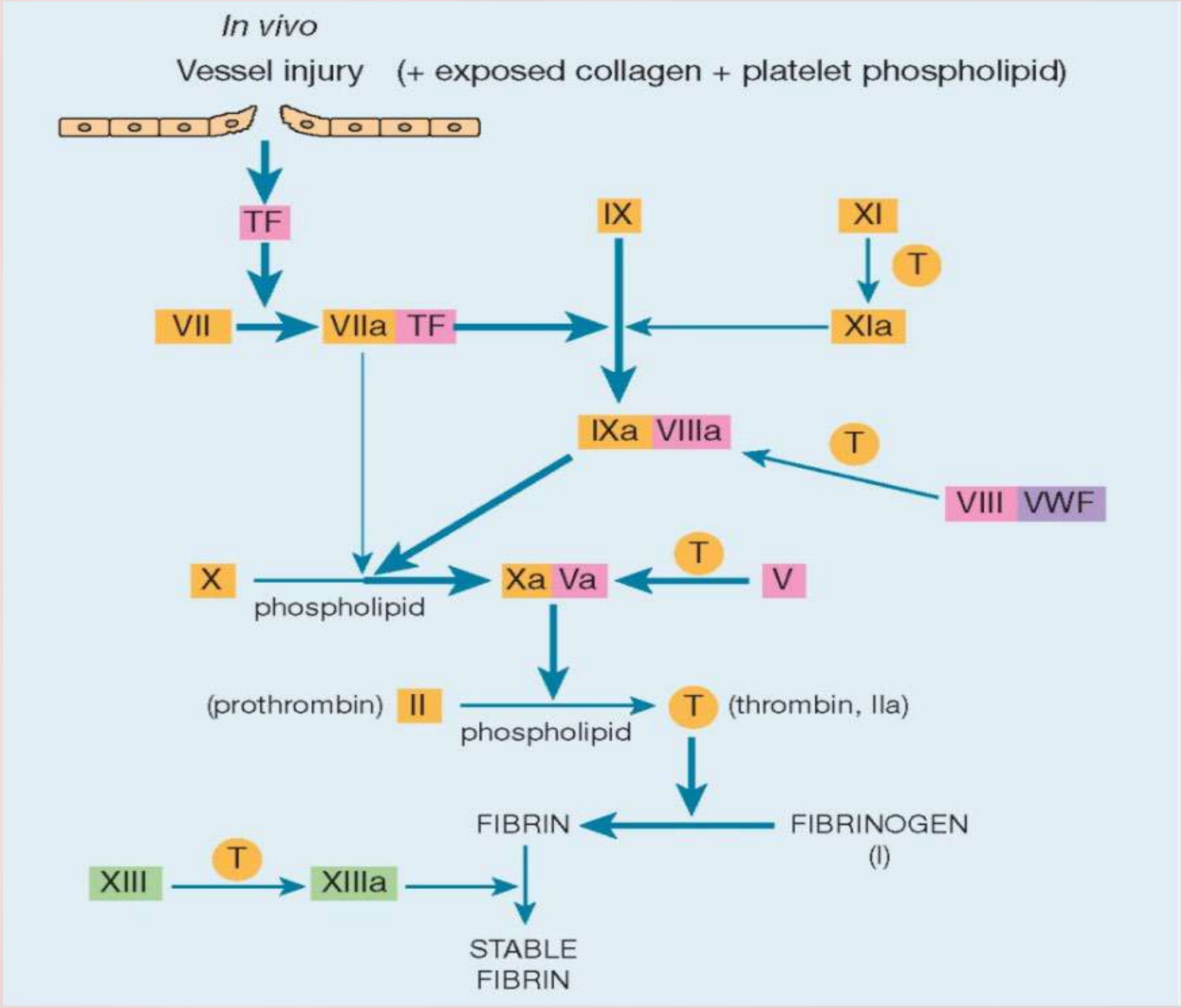


Mechanism of platelet action and formation of primary plug

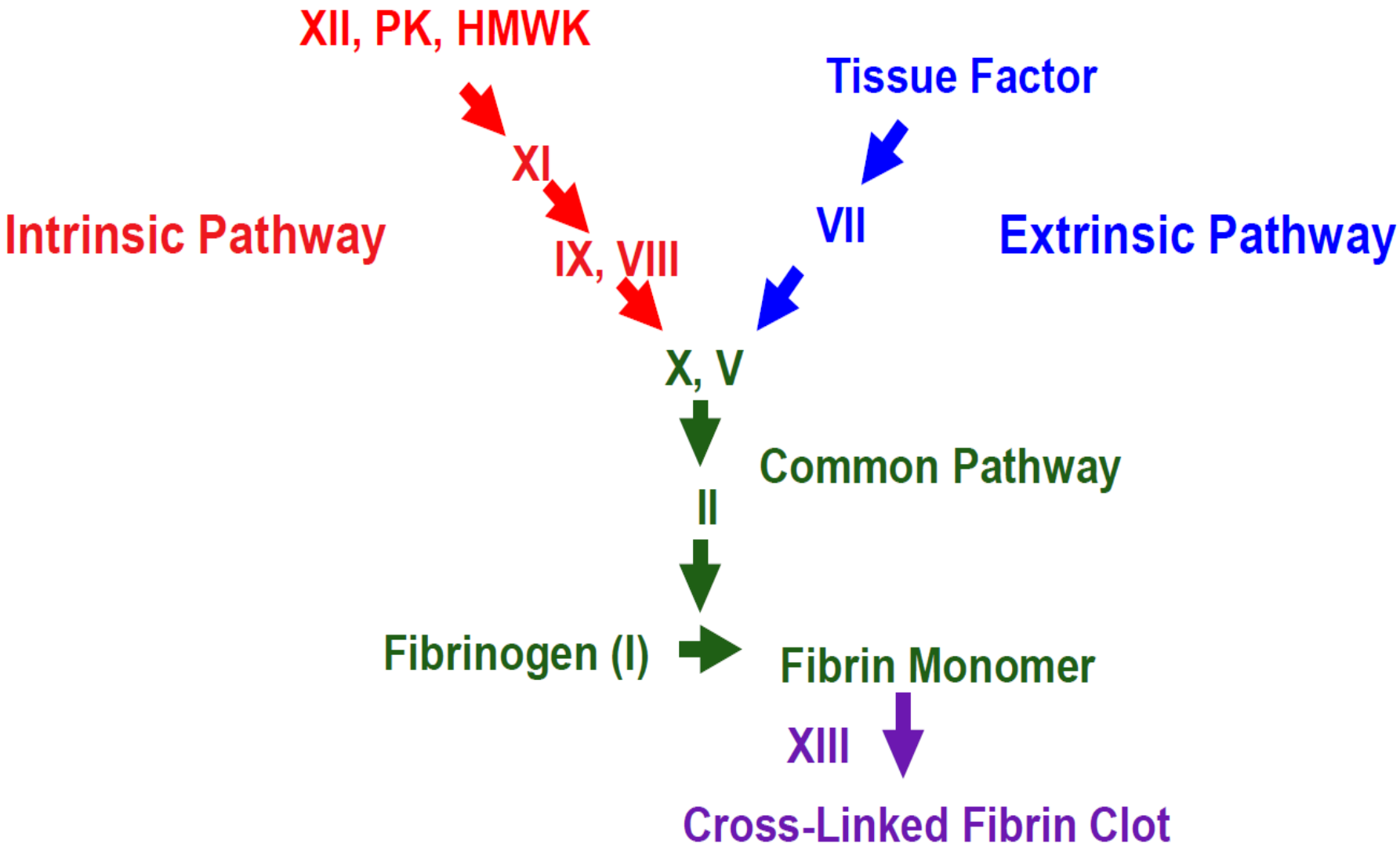
3- Coagulation Cascade:

The pathway of blood coagulation initiated by tissue factor (TF) released from the cell surface after the injury.

When binds with factor VII leads to fibrin formation. Thrombin also activates factors VIII and V amplify the pathway



Current Model of the Intrinsic/Extrinsic Pathways *In Vitro*



Coagulation Factor Inhibitors;

- Important for the limitation of thrombin formation to the injured area
- Starting with tissue factor pathway inhibitor (TFPI) and by the action of antithrombin
- Other inhibitors for the coagulation cofactors, mainly protein C and S.

Fibrinolysis;

- Mainly through the action of plasmin which is activated from plasminogen by the effect of tissue plasminogen activator (TPA, tPA)
- Leading to degradation of the fibrin to fibrinogen degradation products (FDPs).
- Fibrinolytic agents used clinically, mostly streptokinase and TPA.

Tests for Hemostatic Function:

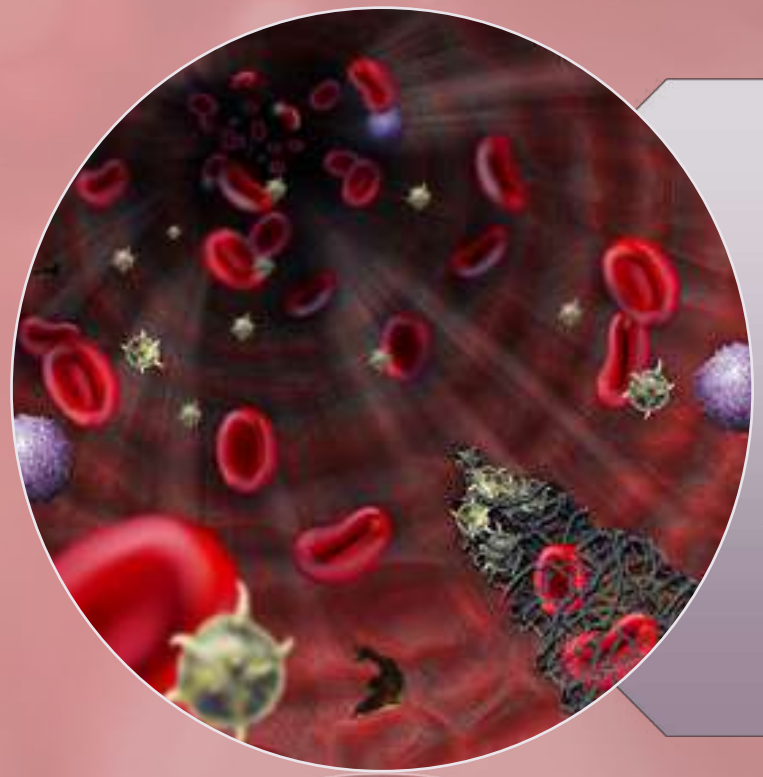
- Vascular disorders
- Thrombocytopenia.
- Blood film for the underlying cause of thrombocytopenia
- Defective coagulation; screening tests for the coagulation

1. Prothrombin time (PT); for factors I (fibrinogen), II (prothrombin), V, VII and X
2. Activated partial thromboplastin time (APTT,PTT); for VII, IX, XI and XII and also, I, II, V and X
3. Thrombin time (TT); for thrombin (IIa) and its inhibitors

- Bleeding time; for platelet function and VWF deficiency
- Platelet function test; mostly by platelet aggregometry and PFA-100 (platelet function analyzer-100; similar use of BT, but more sensitive)
- Test for fibrinolysis; mainly measurement of FDPs, mostly D-dimers.
- Specific factor assay or factor inhibitors.

Notes;

- **Purpura** is a condition of red or purple discolored flat spots on the skin that do not blench on applying pressure.
- The spots are caused by bleeding underneath the skin to the surrounding tissue, secondary to platelet disorders, vascular disorders, coagulation disorders, or other causes.
- It measures 0.3–1 cm (3–10 mm), whereas **Petechiae** intradermal of less than 3 mm (<0.3 cm), and **Ecchymosis** greater than 1 cm.
- **Bruises** are similar to ecchymosis, but it caused by trauma
- **Rashes**; area of irritated or swollen skin. Many rashes are itchy, red, painful, and irritated. Some rashes can also lead to blisters or patches of raw skin.



BLEEDING DISORDERS

BLEEDING DISORDERS

- The bleeding patterns differs according to the cause.
- Result from:

1. Vascular disorders
2. Platelets abnormalities;

- Quantitative; thrombocytopenia.
- Qualitative; abnormal function.

3. Defective coagulation.

	Platelets / Vessel wall diseases	Coagulation diseases
Mucosal bleeding	**Common**	Rare
Petechiae	**Common**	Rare
Deep hematomas	Rare	**Characteristic**
Bleeding from skin cuts	**Persistent**	Minimal
Sex of patient	Equal	>80% male

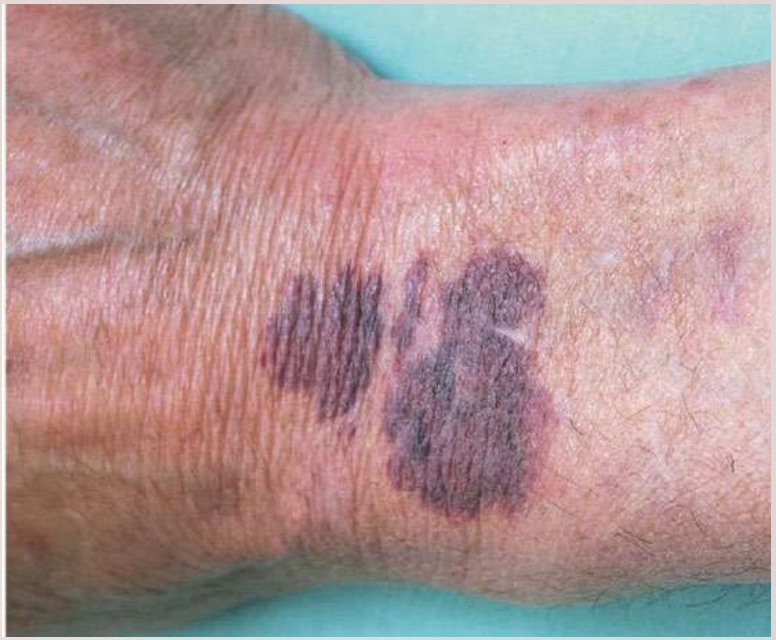
1- Vascular Bleeding Disorders:

Group of disorders characterized by easy bruising and spontaneous bleeding from small vessels, mainly of the skin causing; petechiae and/or ecchymosis.

- Bleeding mucous membranes may be a feature.
- There is no abnormality of the hemostasis laboratory findings;

1. Bleeding time (BT)
2. Prothrombin time (PT)
3. Activated partial thrombin time (APTT).

❖Acquired Vascular defects;



- **Increased Vessel Fragility;**

Women of child bearing age; fragile capillaries

- **Senile purpura**; Benign condition characterized by recurrent formation of purple ecchymoses on the dorsal aspect of forearms and may following minor trauma (bruises), usually in old age group.
- Infections leading to DIC or immune reaction.
- Scurvy and steroid therapy.
- **Henoch-Schönlein purpura**; post acute childhood respiratory tract infection. It's a self-limiting Ig-A mediated immune vasculitis. Characterized by itching purpuric rash at the buttocks and limbs, with painful joint swelling. Hematuria and renal impairment may occur.

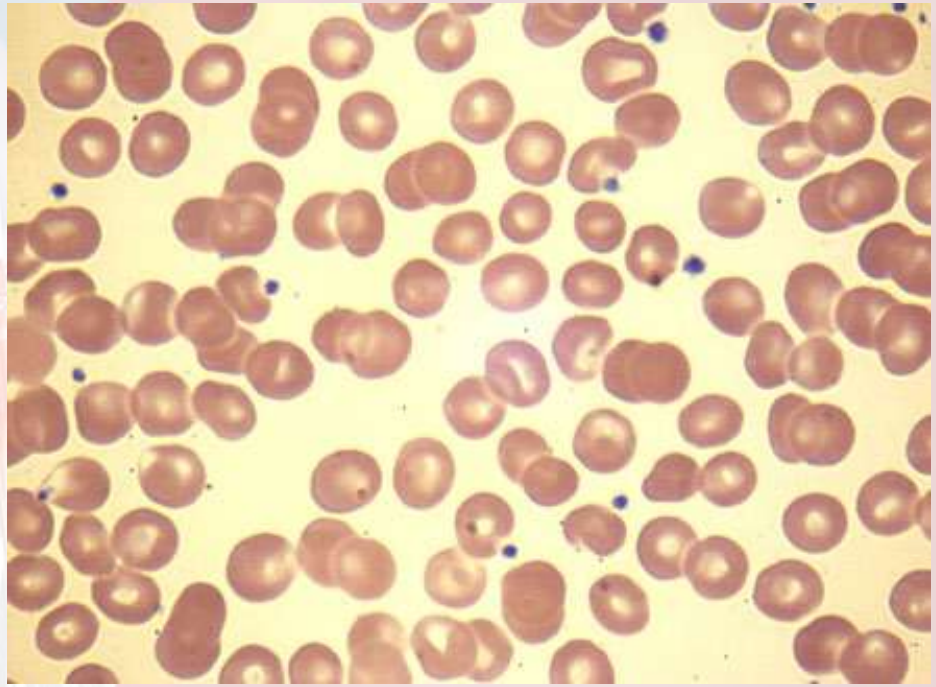
❖Inherited

- Uncommon
- Hereditary hemorrhagic telangiectasia
- Connective tissue disorders; e.g; Marfan's syndrome and Ehlers-Danlos syndrome
- Giant cavernous hemangioma.

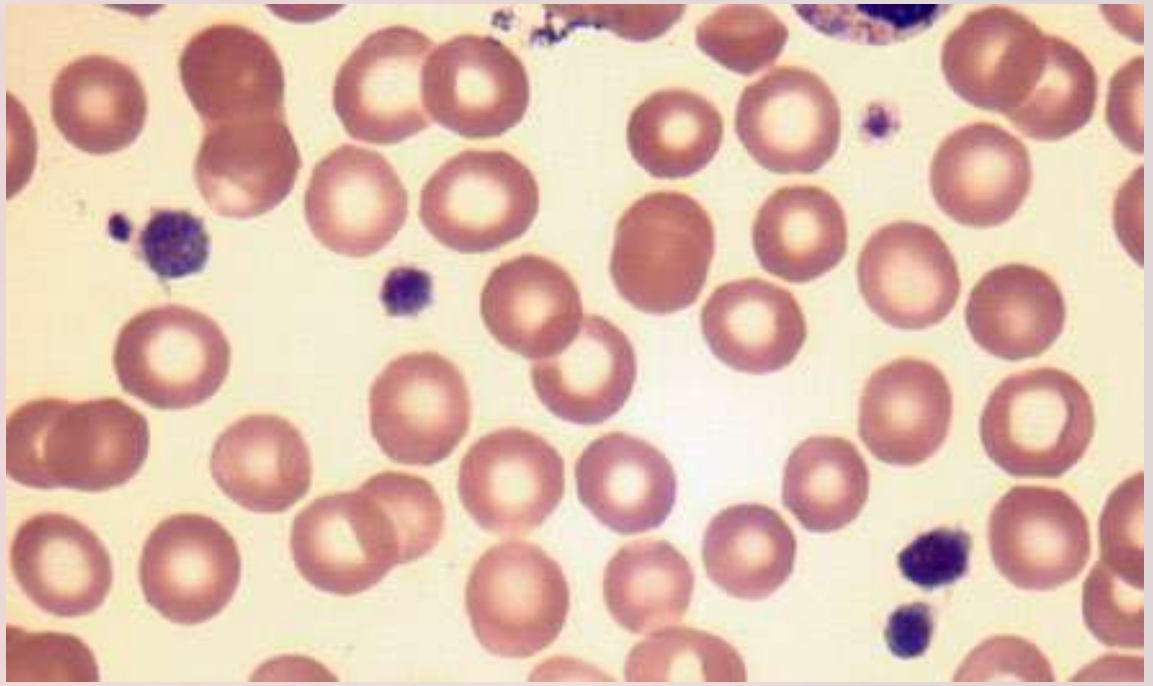
2- THROMBOCYTOPENIA

Reduced platelets count bellow the normal level (NR;150-450×10^9/L)

- The reference range is 150.000 – 450.000 /mm^3.
- Spontaneous bleeding when count falls below 20,000/mm^3.
- Platelet counts in the range of 20,000 to 50,000/mm^3 may lead to post-traumatic bleeding.
- Petechiae or large ecchymoses are commonly found in the skin and the mucous membranes of the gastrointestinal and urinary tracts, but no site is excluded.
- CNS constitutes a major hazard in patients whose platelet count is markedly depressed.
- A prolonged bleeding time with normal PT and APTT.



Normal peripheral blood



Abnormally large platelets

❖Causes of thrombocytopenia;

1- Failure of platelet production

- Selective megakaryocyte depression; drugs, chemicals, viral infections and rarely congenital defects
- Part of general bone marrow failure;

1. Aplastic anemia
2. Leukemia, multiple myeloma,
3. Myelodysplastic syndromes, myelofibrosis
4. Marrow infiltration (e.g. carcinoma, lymphoma, Gaucher's disease)
5. Megaloblastic anemia
6. HIV infection

2- Increased consumption of platelets

- ***Immune***

- Autoimmune
  - Idiopathic; (ITP)
  - Systemic lupus erythematosus (SLE), CLL or lymphoma
  - Infections: *Helicobacter pylori*, HIV, other viruses, malaria
- Drug-induced, e.g. heparin or Immune post-transfusion purpura
- ***Disseminated intravascular coagulation (DIC), Thrombotic thrombocytopenic purpura (TTP) and Hemolytic Uremic Syndrome (HUS)***

3- Abnormal distribution of platelets; *Splenomegaly (e.g. liver disease).* may be up 90% of platelets sequestrated 'pooling'

4- Dilutional loss; *Massive transfusion of stored blood.* Massive transfusion syndrome (> 10 units of blood per 24 hours), due to lack of the platelets in the stored blood units for more than 24 hours.

Increased Platelets Destruction:

Autoimmune (Idiopathic) Thrombocytopenic Purpura (ITP):

❑ Chronic ITP:

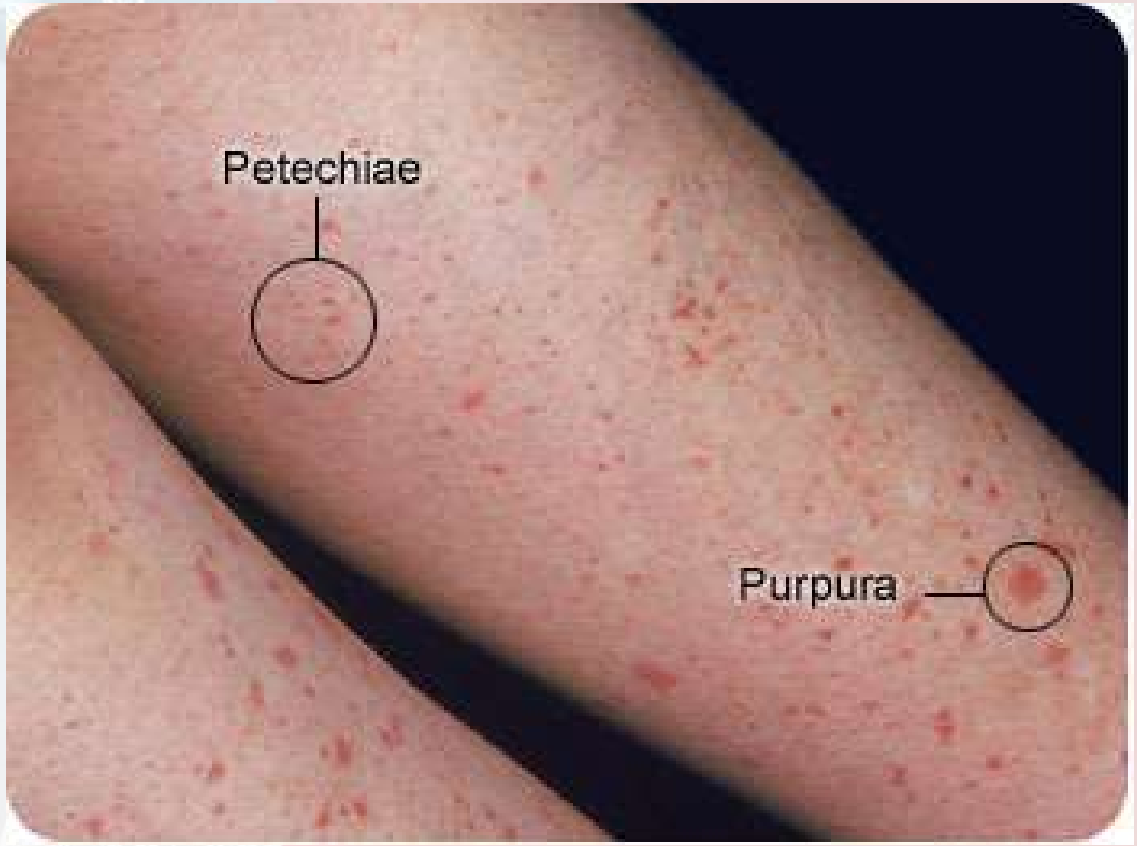
- Most common cause of thrombocytopenia
- No anemia or neutropenia
- Affecting women more than men 15-50 years old
- Mostly idiopathic and may be due to other causes
- Usually associated with shortening of platelet life span up to few hours (NR; 7-10 days).

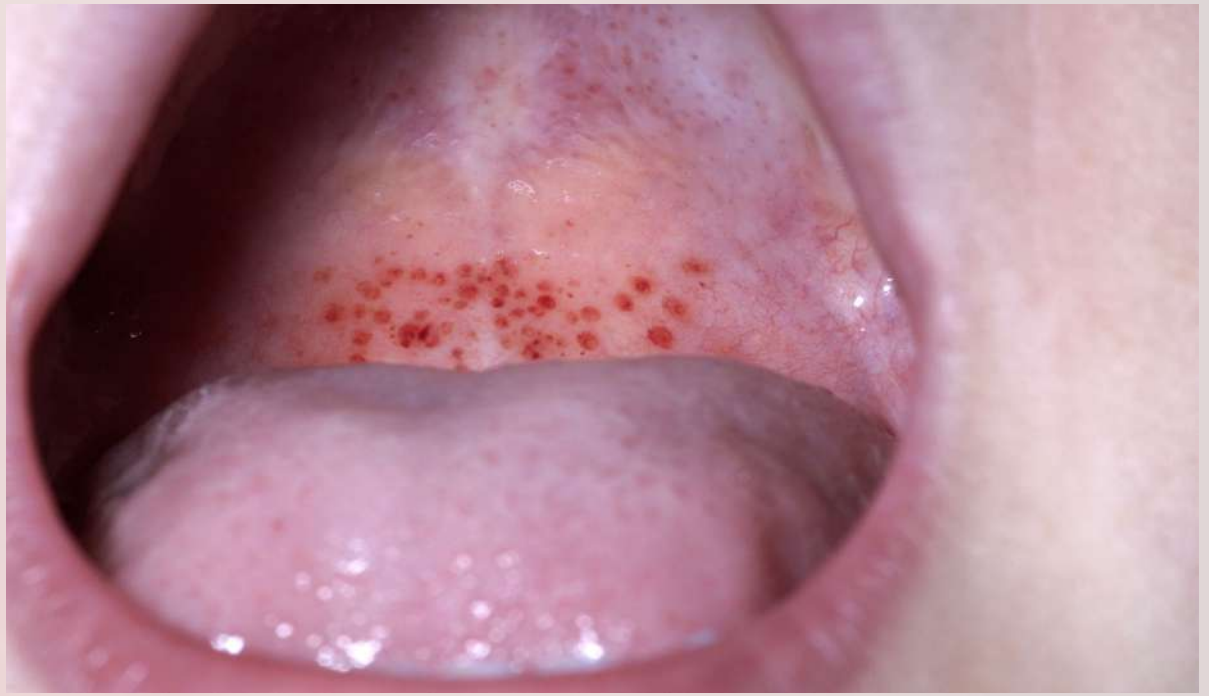
❖Clinical Features;

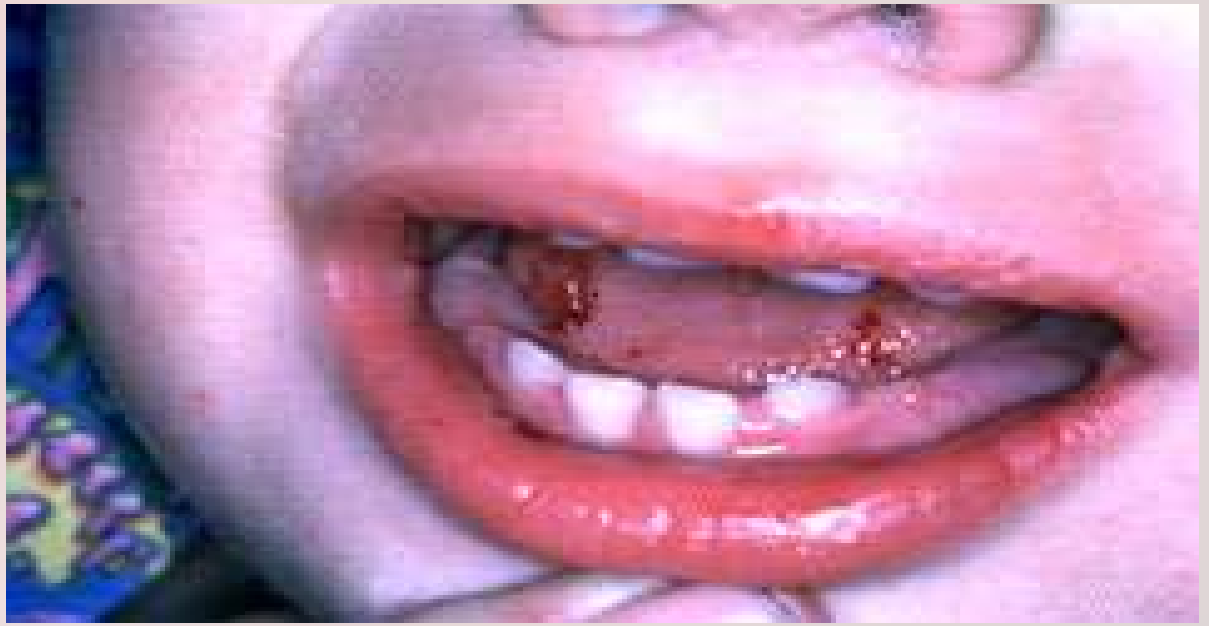
- Asymptomatic.
- Insidious onset.
- Petechiae, and easy bruising.
- Menorrhagia in women.
- Mucosal hemorrhage in severe cases.
- Severity of the hemorrhage is less than that due to BM suppression of the relatively same degree of thrombocytopenia, because of the circulating young platelets.

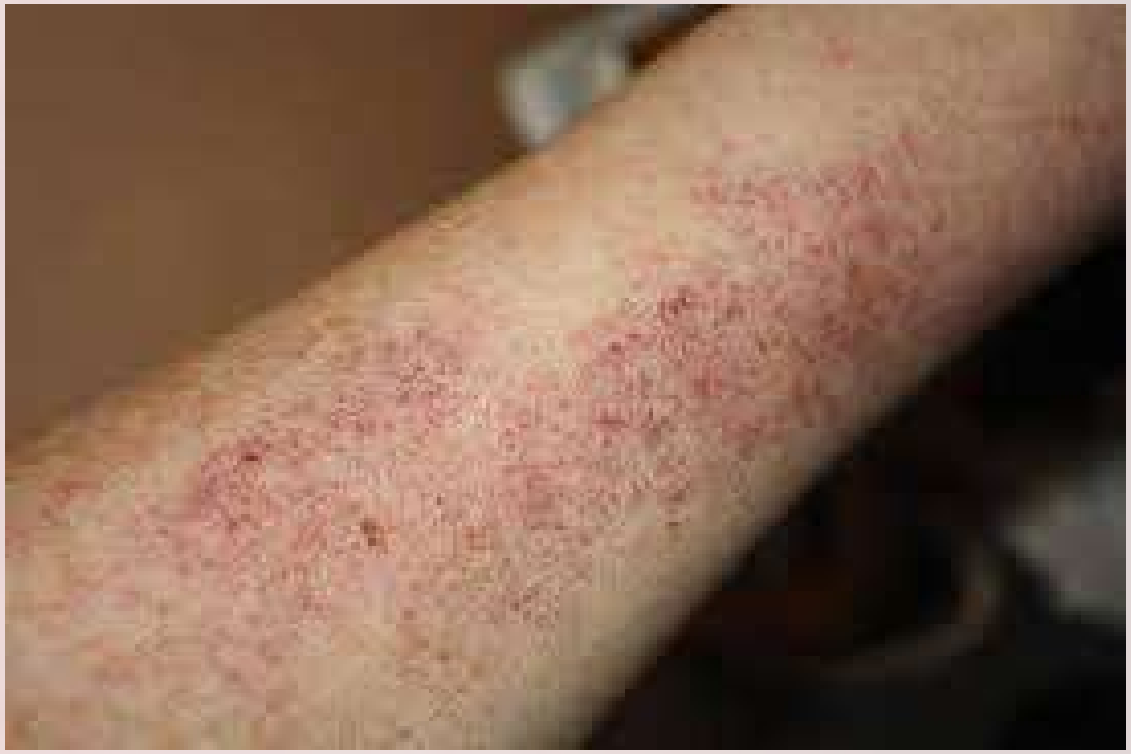
❑ Acute ITP:

- Most common in children
- Mostly following vaccination or viral infection
- **No other abnormality** apart from thrombocytopenia and diagnosed by exclusion
- If BMA performed; shows increased megakaryocytes production
- Usually **benign** course with spontaneous remission and may become chronic
- **No** need for treatment, unless platelet count **bellow** 20×10^9/L, usually with steroids and/or immunoglobulin.
- The diagnosis by exclusion of other causes of thrombocytopenia


Petechiae
Purpura

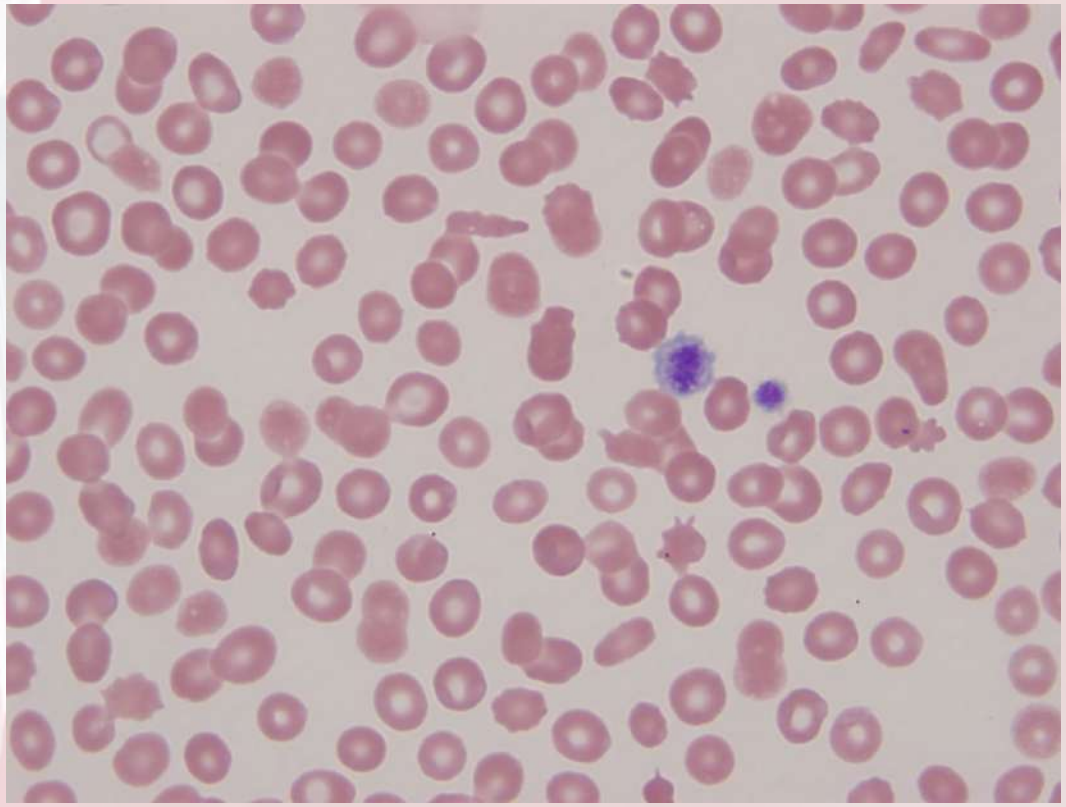


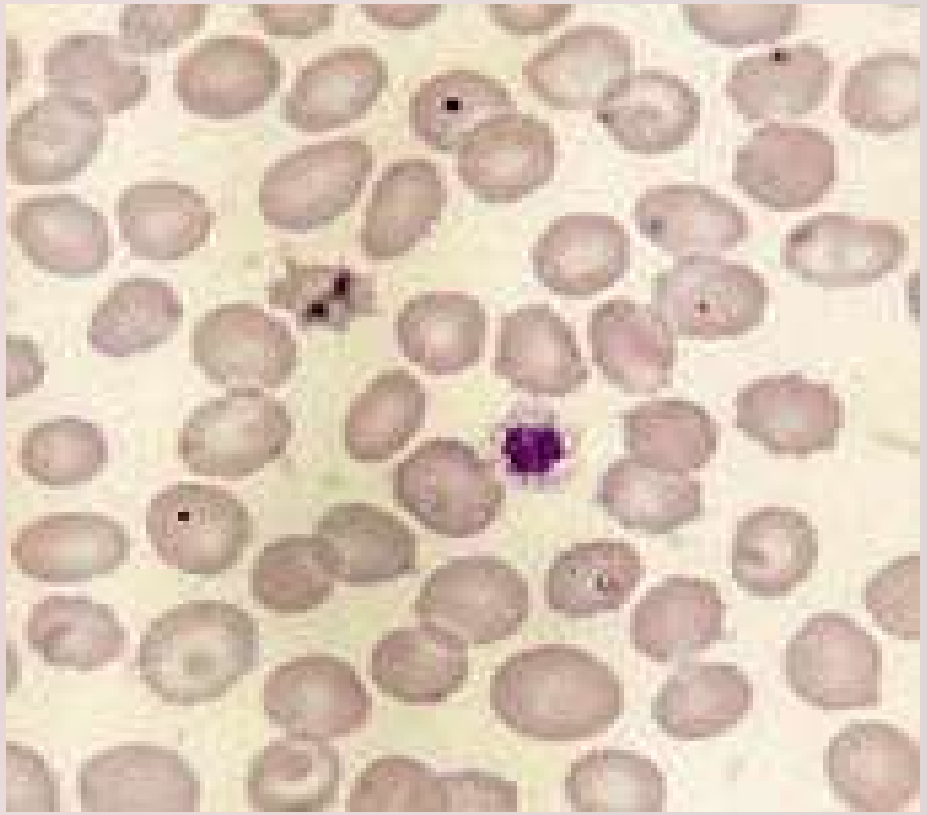


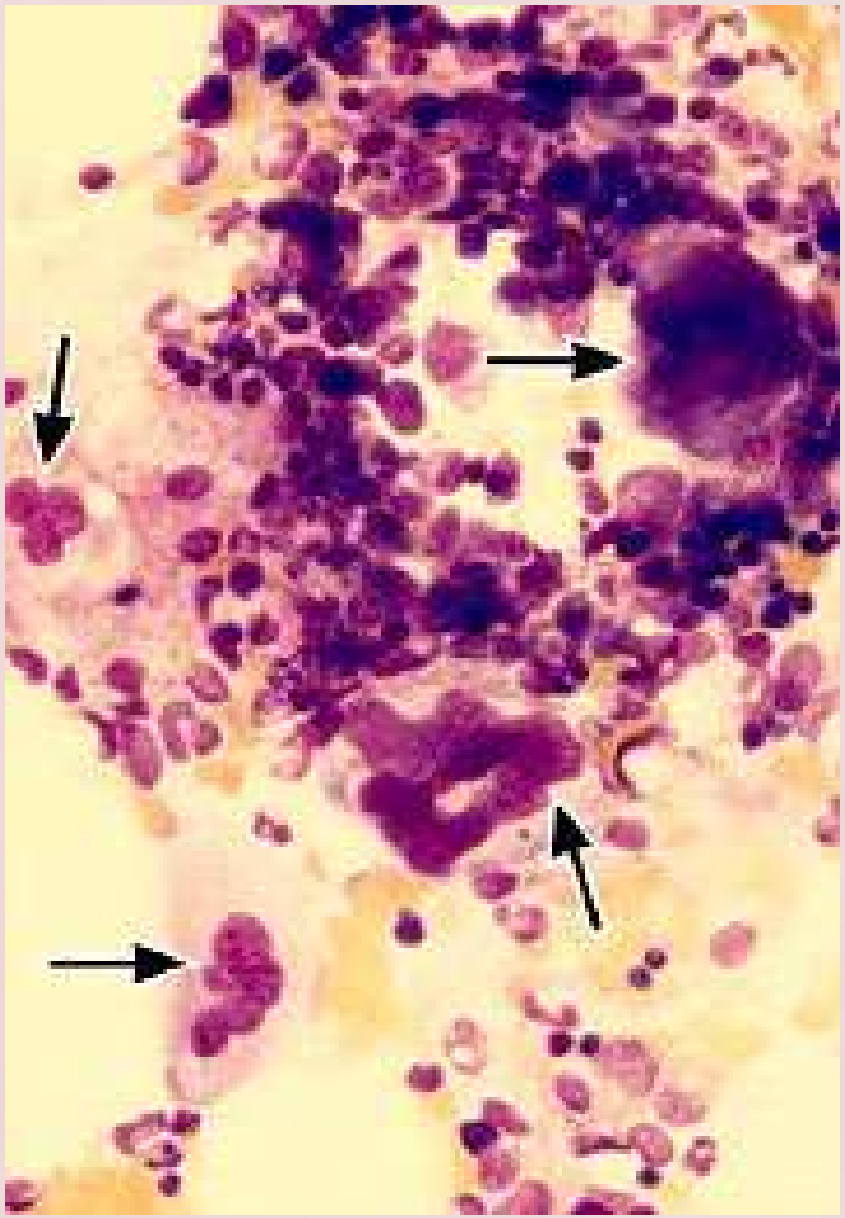


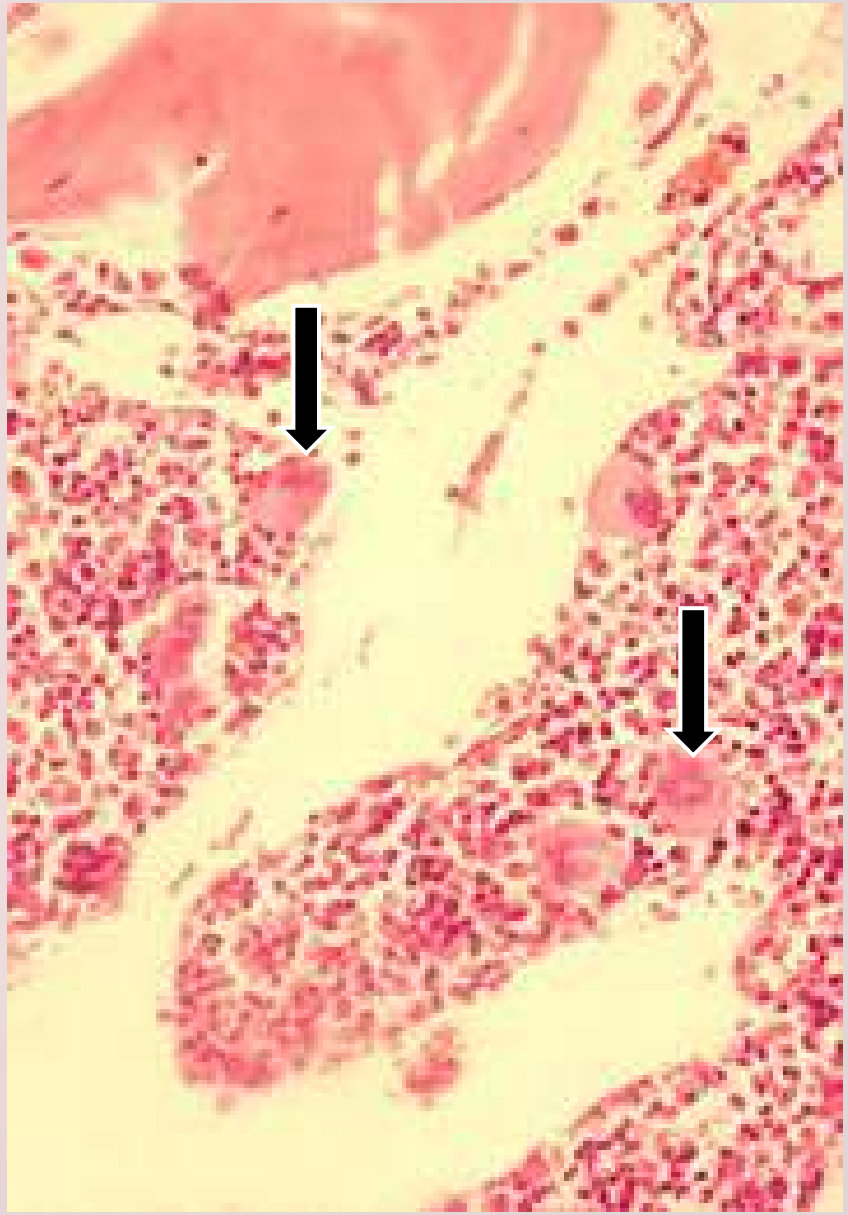
❖Laboratory Findings;

- Low platelet count.
- Blood film; showing thrombocytopenia and a giant platelet.
- Normal or increased BM megakaryocytes, usually of normal morphology









BM (aspirate, left and biopsy, right) Megakaryocytes (arrow) are normal or increased BM, usually of normal morphology

❖Treatment;

The aim is to achieve the platelets in a level not associated with bleeding (50×10^9/L), at this level usually does not require treatment

- Platelet transfusion in life-threating bleeding
- Corticosteroids
- Immunoglobulins
- Immunosuppression
- monoclonal Ab
- Stem cell transplantation may cure sever cases

Disorders of Platelets Function:

❖Hereditary Disorders:

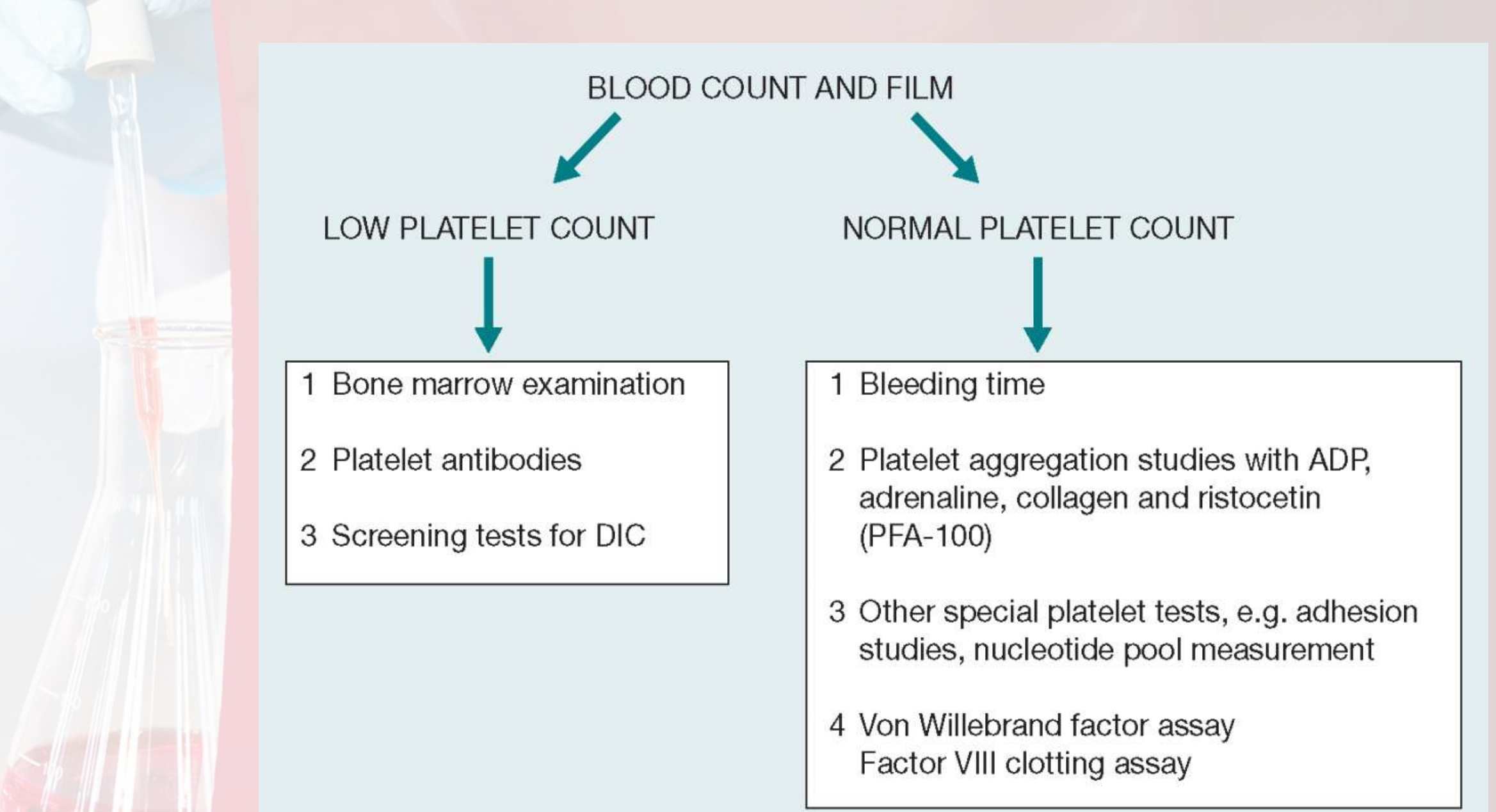
- Von Willebrand disease (VWD)
- Rare disorders; Thrombasthenia (Glanzmann's disease) and Bernard-Soulier syndrome and platelet storage pool disorders.

❖Acquired Disorders;

1. Antiplatelets drugs;
2. Aspirin (most common cause of platelet dysfunction), and its effect may be for 5-7 days.
3. MP disorders and Uremia.

❖Laboratory Diagnosis;

- Blood count and bd film
- BM examination; to distinguish between marrow failure or peripheral consumption
- Prolonged BT; (NR; 2-7 min)
- Coagulation screening test; usually normal
- Platelet antibodies screening and platelet function tests; mainly platelet aggregation and PFA-100



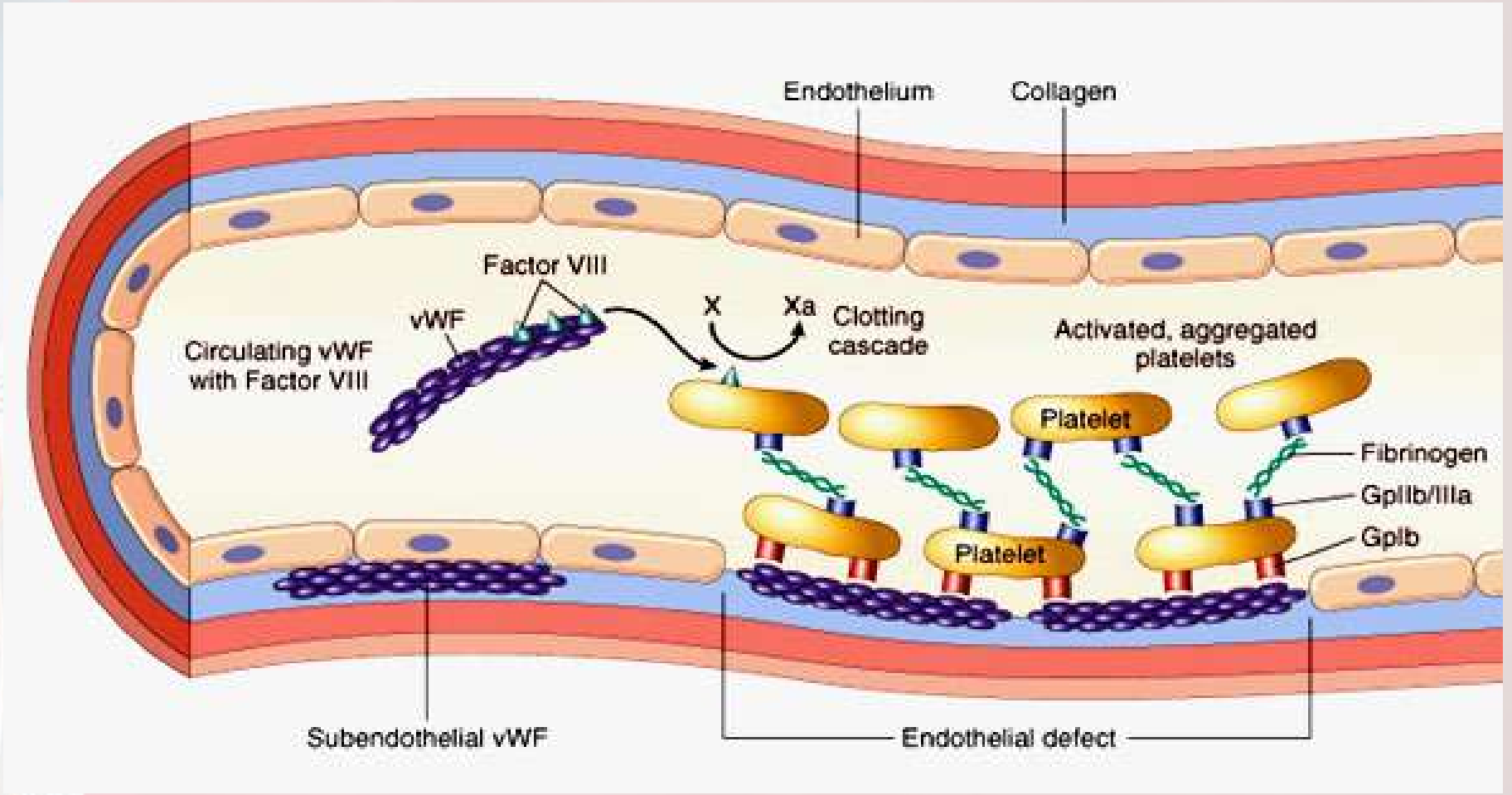
Diagnosis of platelets bleeding disorders

COAGULATION DISORDERS

Either hereditary or acquired

1- Hereditary Coagulation Disorders;

- Hereditary coagulation disorders are a major problem of bleeding manifestations
- Most common; Hemophilia A (FVIII deficiency)
- Von Willebrand disease (VWD)
- Hemophilia B (Christmas disease, FIX deficiency)
- Other are rare; F VII, X and XIII deficiency occur as autosomal recessive disorders, associated with umbilical stump and intracranial hemorrhage bleeding. FXI deficiency may also occur



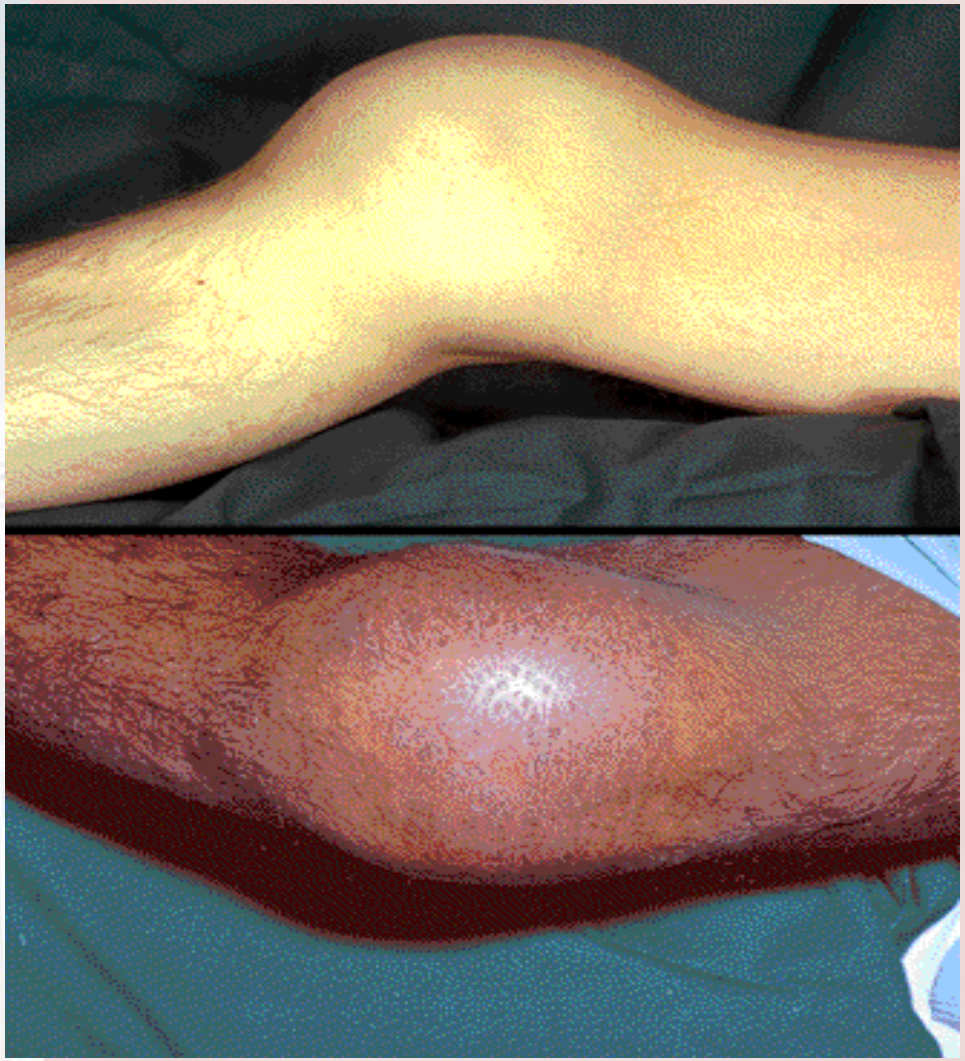
Hemophilia A and vWD are two of the most common inherited disorders of bleeding, are caused by qualitative or quantitative defects involving FVIII/vWF complex. A component which is required for the activation of factor X in the intrinsic coagulation pathway, is called FVIII procoagulant protein, or FVIII:C.

Hemophilia A (FVIII Deficiency)

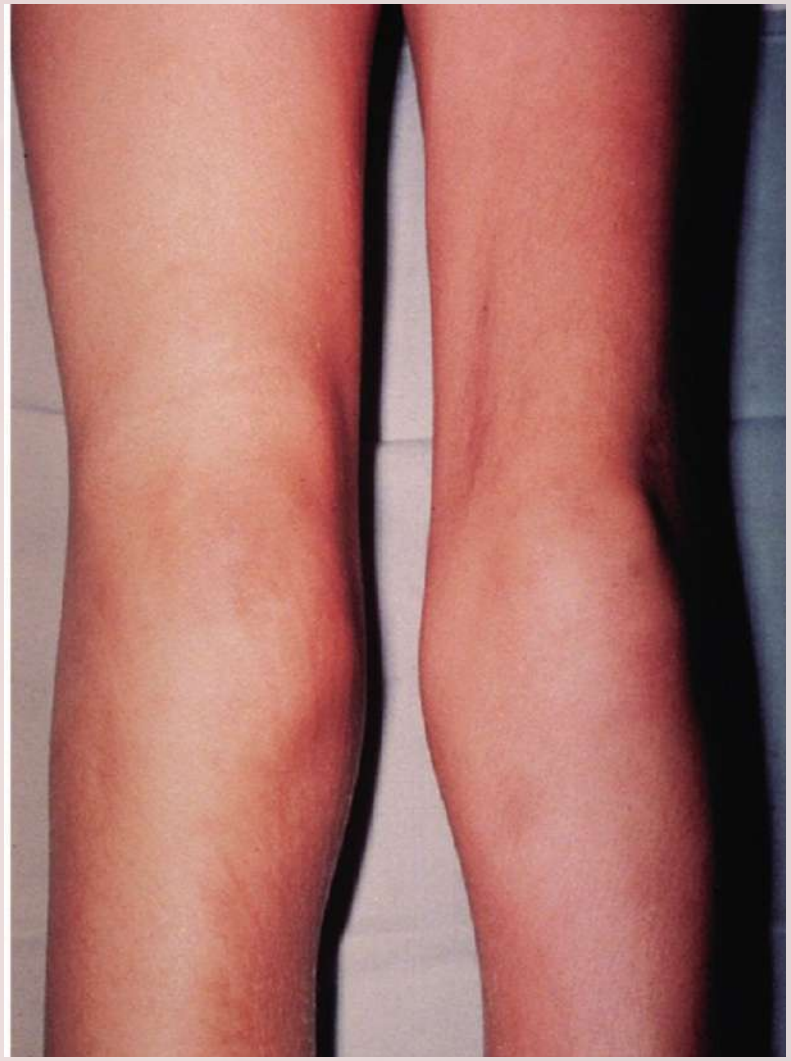
- Most common inherited factor deficiency.
- It is a sex-linked recessive trait (affecting males or homozygous females), but in one third develop mutation with no family history
- There are different types of mutations leading to difference in the factor level and disease severity.

❖ Clinical features;

- Severity depends on FVIII level, sever form level of <1%, moderate 1-5% and in mild >5%.
- Profound bleeding after circumcision or soft tissue and excessive soft tissue (bruising) after minor trauma.
- Muscle hematoma and joint bleeding (hemarthrosis) leading to joint contracture and muscle wasting



Severe Haemophilia A; gross swelling of the knee joints of acute hemarthrosis.



Acute hemarthrosis of the right knee joint with swelling of the suprapatellar region. There is wasting of the quadriceps muscles, particularly on the left

- Prolonged bleeding after tooth extraction
- Mucosal bleeding of renal tract (hematuria)or GIT and CNS bleeding
- Pseudotumors; due to encapsulated hematomas
- HIV infection and hepatitis; due to infected F VIII.

❖ **Laboratory Findings;**

- APTT; prolonged (NR; 26-40 sec), corrected by addition of normal plasma if there is no F VIII antibodies.
- Factor VIII assay; the level in sever disease; <1%, in moderate disease; 1-5% and in mild disease; >5%
- Normal BT, PT and platelet function
- DNA analysis; useful for the detection of carrier state

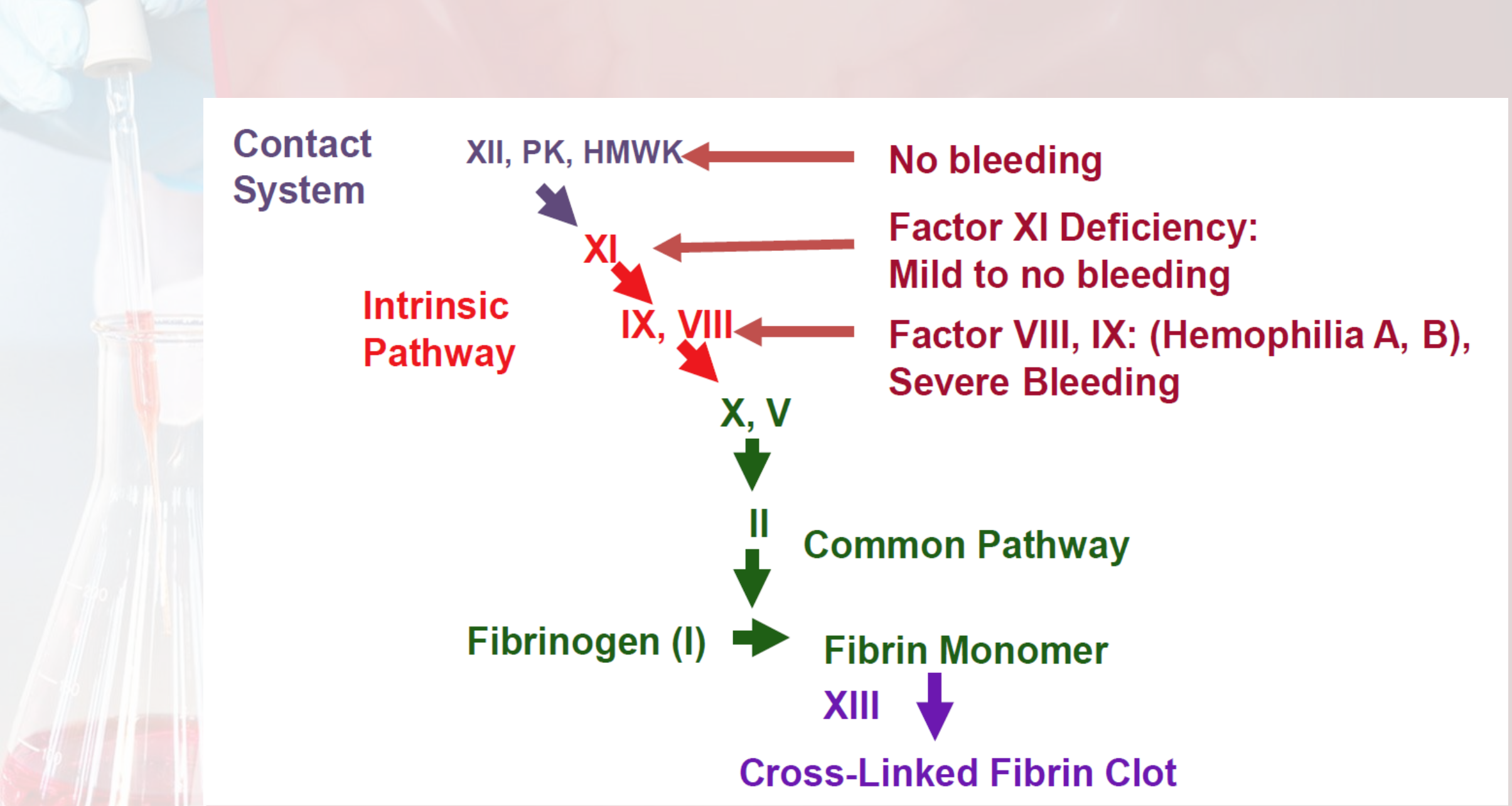
❖ Treatment;

- Hemophilia center is an important specialized place
- Factor VIII infusion, recombinant factor VIII; usually control of the bleeding at factor level of 30-50%
- Local treatment of the affected area
- Prophylactic treatment; factor VIII used for the patients with severe disease, and a special care for any minor or major operation including dental operations
- Gene therapy; under trials

Hemophilia B (F IX deficiency/Christmas Disease) and von Willebrand Disease (VWD)

- Other less common hereditary coagulation disorders.
- Hemophilia B usually unrecognizable clinically from Hemophilia A. only possible be differentiated by assay of the factor IX level. And its treatment involves infusion of recombinant factor IX, now widely available.
- VWD; may shows more possibility of skin bleeding than Hemophilia A and B.
- The laboratory findings are the best for the differentiation of the diagnosis.

	Hemophilia A	Hemophilia B	VWD
Inheritance	Sex-linked	Sex-linked	Dominant (incomplete)
Main sites of hemorrhage	Muscle, joints, post-trauma or postoperative	Muscle, joints, post-trauma or postoperative	**Mucous membranes, skin cuts**, post-trauma or postop
Platelet count	Normal	Normal	Normal
BT & PFA-100	Normal	Normal	**Prolonged**
PT	Normal	Normal	Normal
APTT	**Prolonged**	**Prolonged**	**Prolonged or normal**
Factor VIII	Low	**Normal**	moderately reduced
Factor IX	Normal	**Low**	Normal
VWF	Normal	Normal	**Low or abnormal function**
Platelet aggregation	Normal	Normal	**Impaired**


Contact System
XII, PK, HMWK
No bleeding
XI
Factor XI Deficiency:
Mild to no bleeding
Intrinsic Pathway
IX, VIII
Factor VIII, IX: (Hemophilia A, B),
Severe Bleeding
X, V
II
Common Pathway
Fibrinogen (I)
Fibrin Monomer
XIII
Cross-Linked Fibrin Clot

2- Acquired Coagulation Disorders

- The liver is the site of synthesis of several coagulation factors; thus, parenchymal diseases of the liver are common causes of hemorrhagic diatheses.
- vitamin K deficiency may be associated with a severe coagulation defect, because this nutrient is essential for the synthesis of prothrombin (II) and clotting factors VII, IX, and X.
- Several liver diseases are associated with complex derangements of platelet function and fibrinogen metabolism, all of which contribute to the coagulopathy in liver disease.

❖***Deficiency of vitamin K-dependent factors***

- Hemorrhagic disease of the newborn
- Biliary obstruction and chronic Liver disease
- Malabsorption of vitamin K (e.g. tropical sprue, gluten-induced enteropathy)
- Vitamin K-antagonist therapy
- Disseminated intravascular coagulation (DIC); consumption of all clotting factors and platelets

❖***Inhibition of coagulation***

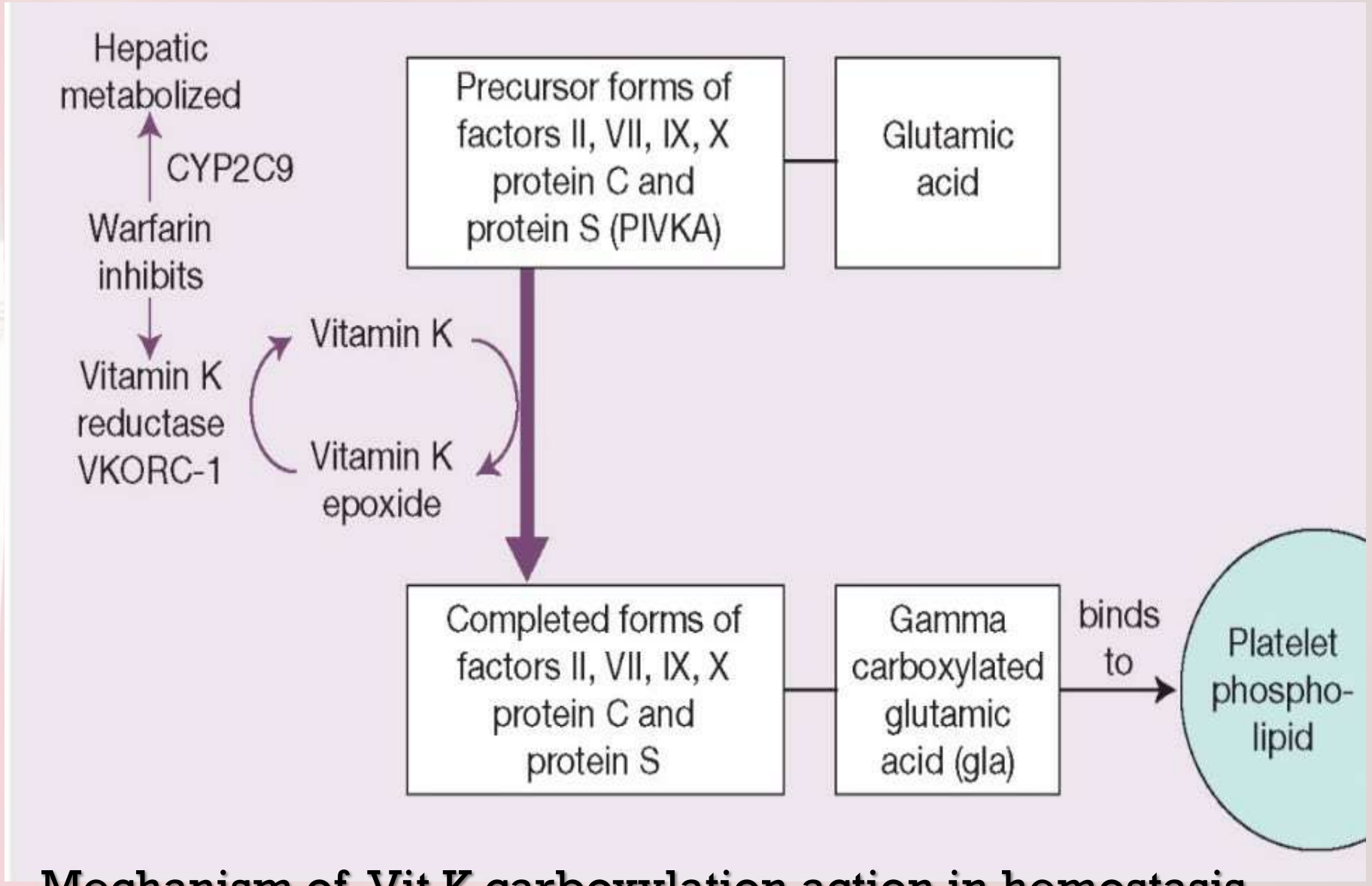
- Specific inhibitors (e.g. antibodies against factor VIII)
- Non-specific inhibitors (e.g; SLE and RA)

❖***Others;***

- Diseases with M-protein production that interfere with hemostasis
- Therapy with heparin, defibrinating agents or thrombolytics
- Massive blood transfusion syndrome

Vitamin K Deficiency

- Fat-soluble vitamin (vit.), obtained from green vegetable and bacterial synthesis in GIT
- Important for the complete form of the clotting factors; II, VII, IX and X, in addition to proteins C and S
- Its absence leads to impaired function of these Vit.K- dependent factors.



Mechanism of Vit K carboxylation action in hemostasis

Hemorrhagic Disease of the Newborn

- Vit.K-dependent factors are low at birth.
- Further fall in breast-fed infants.
- Liver immaturity and lack of bacterial gut responsible for vit.K synthesis.
- Usually develops at 2-4th day of life.
- PT and APTT both high.
- Normal platelets, fibrin and FDPs.
- **Treated** by vit K injections.

Disseminated Intravascular Coagulation (DIC)

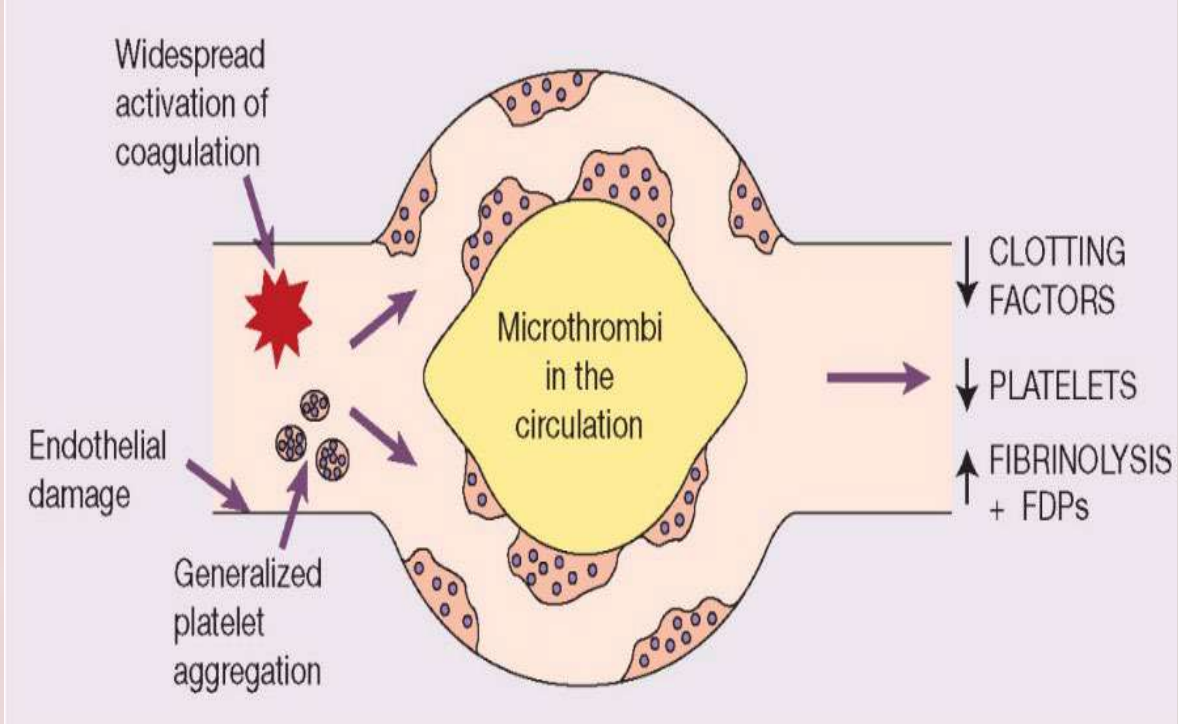
Wide spread intravascular deposition of fibrin associated with consumption of platelets and coagulation factors

- Due to;

1- Circulating procoagulants.

2- Wide spread endothelial damage

3- Platelet aggregation.



1- Infections; septicemia (gram-negative, meningococcal and *Clostridium welchii*) and viral infection; (varicella, HIV, hepatitis….).

***2- Malignancy*;** Widespread mucin-secreting adenocarcinoma and AML-M3

3- Obstetric complications; amniotic fluid embolism, Eclampsia and Septic abortion

***4- Hypersensitivity reactions*;** Anaphylaxis and incompatible blood transfusion

4- Widespread tissue damage; following surgery or trauma and Severe burns

5- Vascular abnormalities; leaking prosthetic valves, cardiac bypass surgery and vascular aneurysms .

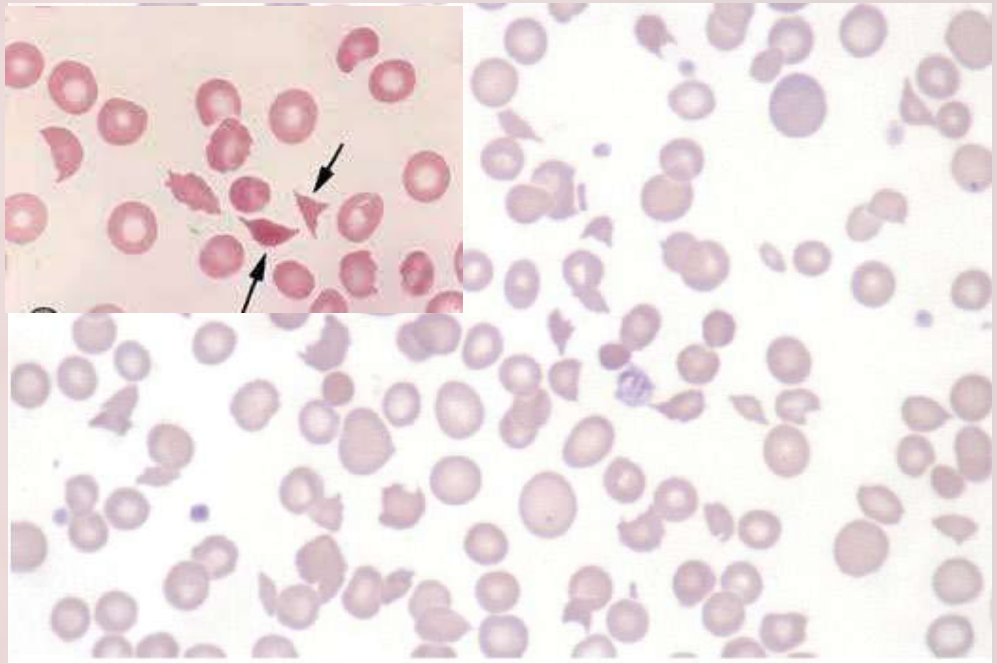
6- Others; Liver failure, Pancreatitis, Venoms, Massive blood loss

❖Clinical Features

- Combination of wide spread bleedings and
- Microthrombi of retina, skin, fingers and CNS ischemia
- May transforms to chronic form.

❖Laboratory Features

- Platelets are low
- PT, APTT, and TT all are prolonged
- Fibrinogen is low
- FDPs; D-dimers in serum and urine



- Blood film; characteristic RBCs show prominence of schistocytes (fragmented cells) by the effect of fibrin strand in the small vessels with low platelet count

COVID-19 Coagulopathy vs DIC

DIC, is a generalized consumptive process with microangiopathic hemolytic process, while COVID-19 is a localized process mostly to the lung alveoli.

1. Mild thrombocytopenia.
2. Prothrombin time (PT) not always elevated.
3. Normal activated partial thromboplastin time (aPTT).
4. No microangiopathic hemolytic process.

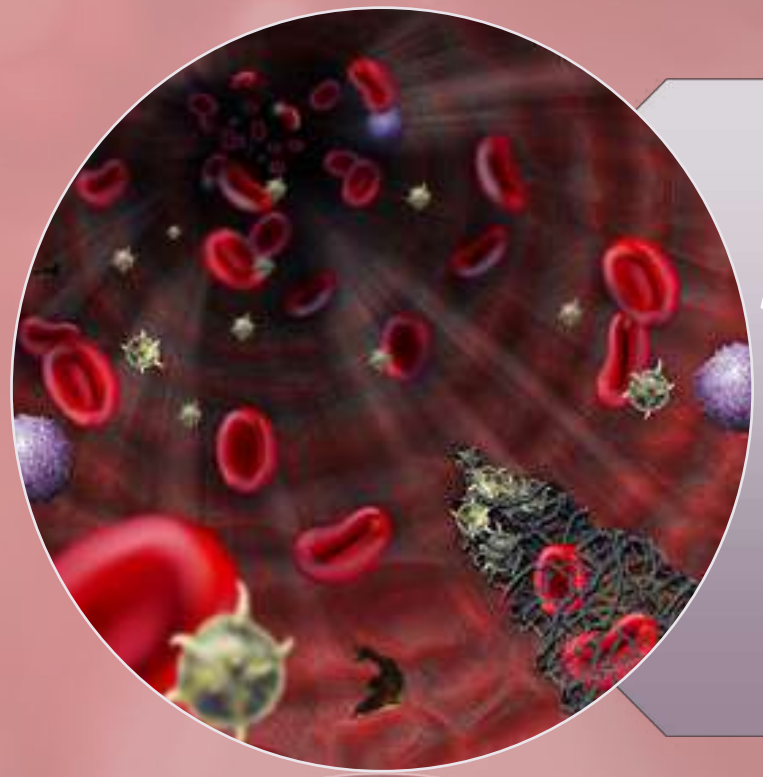
Iba T. et al, *J Thromb Haemost*. 2020;18:2103–2109.

❖Treatment

- Treat underlying cause and usually needs intensive care.
- Bleeding; by sue of blood and its product transfusion;
  - ➢Platelet conc.
  - ➢FFP (fresh frozen plasma)
  - ➢Cryoprecipitate
  - ➢Blood transfusion (RBCs)
- Thrombosis; can be treated by heparin or warfarin and antithrombin.

Other causes;

- **Thrombotic thrombocytopenic purpura** (TTP); may be familial or acquired. An abnormality of formation of small thrombi causing the pool of platelets with occlusion of the microvasculature causing wide spread organs' tissue ischemic, and associated by microangiopathic hemolytic anemia
- **Hemolytic uremic syndrome** (HUS); similar to TTP, but it occurs in children and the ischemia mostly renal



THROMBOTIC DISORDERS

THROMBOSIS

Formation of solid masses of platelets and fibrin in the circulation, which could be arterial or venous, with subsequent ischemia of the distal part or embolization to a distant organs.

❖**Arterial**

- Usually associated with; atherosclerosis of the vessel wall in presence of the following risk factors;
- Hypertension
- Hyperlipidemia,
- DM
- Smoking, …etc.

❖Venous Thrombosis

- Can be hereditary or acquired. Three compartments are important for venous thrombus formation;

1. Slowing down of blood flow
2. Hypercoagulability of the blood
3. Vessel wall damage.

- There is a wide range of risk factors can predispose for such thrombus phenomena.
- The acquired are more common than the hereditary causes

❖ Factors predisposing to thrombosis

1- Patient factors; increasing age , obesity, immobility, oral contraceptives, pregnancy and puerperium.

2- Surgical conditions; major surgery, (abdominal or pelvic surgery, and Major lower limb orthopedic.

3- Haematological disorders; polycythemia vera, essential thrombocythemia, deficiency of anticoagulants (antithrombin, proteins C, and S).

- Antiphospholipid syndrome; Anticardiolipin antibody and Lupus anticoagulant (more strongly associated with thrombosis than anticardiolipin antibodies).

4- Non-hematological medical conditions; myocardial infarction, inflammatory bowel disease, malignancy…etc

❖***Acquired disorders***

- Age, Obesity and Dehydration
- Varicose veins
- Pregnancy, puerperium and estrogen therapy (oral contraceptive and other hormones)
- Hyperviscosity (polycythemia)
- Stroke and Surgery; especially abdominal, hip and major orthopedic surgery
- Major trauma and Acutely ill hospitalized medical patients
- Lupus anticoagulant and Heparin-induced thrombocytopenia
- Malignancy and Myeloproliferative disease

❖***Hereditary hemostatic disorders***

- Proteins C and S and Antithrombin deficiency
- Dysfibrinogenemia
- ABO blood group (individuals of non-O group are more liable than group O)

Deep Venous Thrombosis;

Formation of one or more blood clots (thrombi) in one of the body's large veins, most commonly in the lower limbs (e.g., lower leg or calf).

- **Clinically** the patient with one or more of the predisposing factors, develops unilateral thigh or calf swelling or tenderness with pitting edema.
- **Ultrasound** and doppler study can be diagnostic and contrast study (venography) reserved to negative result of ultrasonic examination.
- **MRI**; but not routinely as its expensive procedure.

Treatment

- Urgently as it may lead to serious sequalae, such as pulmonary embolism
- Anticoagulants; stating with heparin injections or the low molecular weight of heparin (LMWH)
- Followed by oral warfarin, which needs a dose control by PT test and measured according to INR (2.0-2.5)
- ***INR;*** *International Normal Ratio; which calculated as a ratio of patient's PT to the mean of control PT, because of the normal variability of PT test*


Thank You
Merci
Gracias
Spacibo
Danke
Hvala
Arigato
Kam Sah Hamnida
Xièxie
Mèsi
Chokrane
Dziakuju
Aabhar
Takk
aDank
Buznyg
ThintKo
Blagodaram
Matondo
Mercé
Taiku
Dakujem
Terima Kasih
Rahmat
Tanemirt
Tenki
Gràcies
Faleminderit
Efharisto
Najis Tuke
Grandmerce
Nirringrazzjak
Bayarlalaa
Obrigado
Saha
Salamat
Multumesc
Cám On
Gracie
GratiasAgo
GratiasAgimus
Barkal
Chnorakaloutioun
Gratzias
Tänan Väga
Ačiū
Dankie
Tak
Sagolun
Motashakkeram
KopKhunKha
شكراً جزيلاً