University of Baghdad
College of Medicine
2024-2025

Title: Bleeding Disorders

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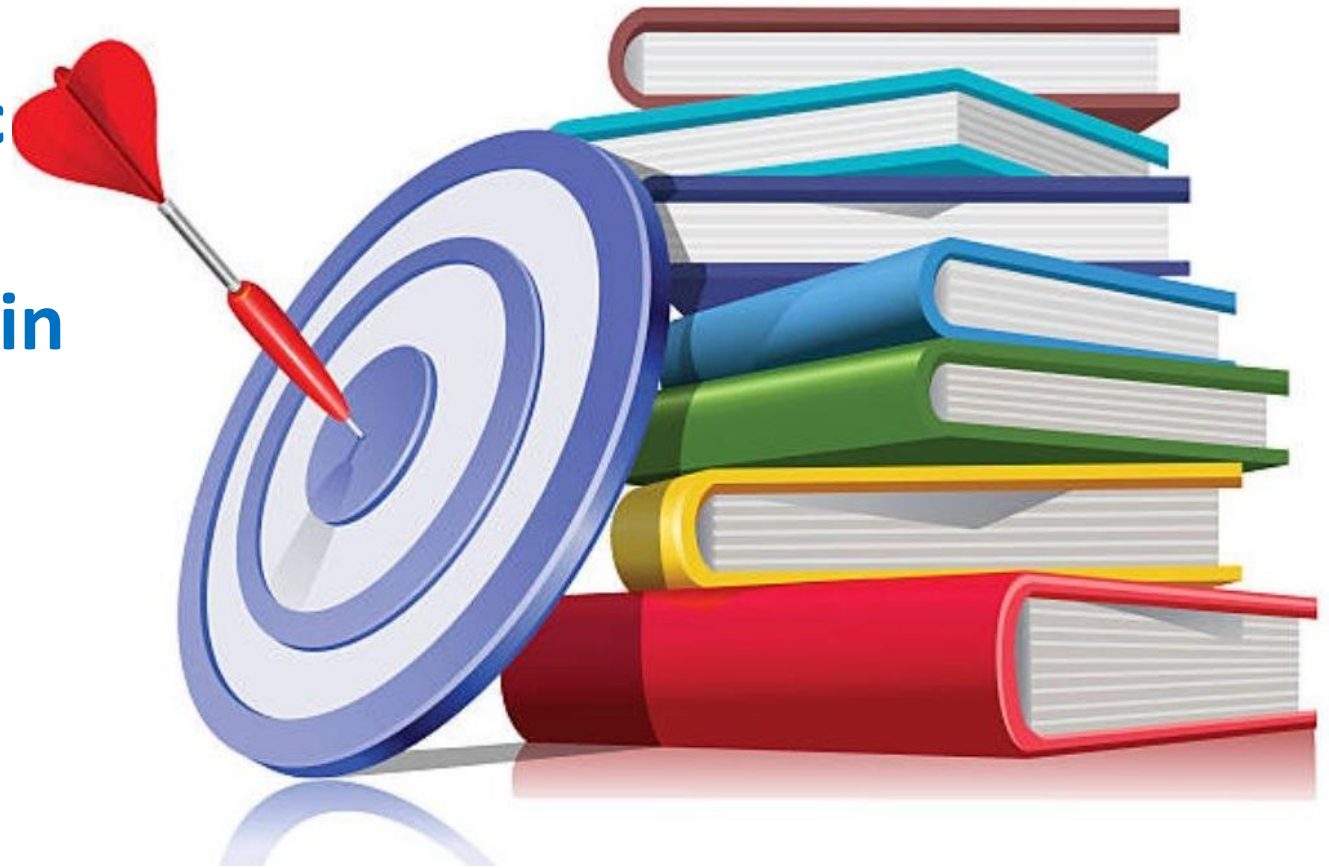
Fourth grade

Date: Oct 2024

Learning objectives

- Define hemostasis.
- Identify the steps of hemostatic response.
- Understand the role of platelet in hemostasis.
- Explain the role of VWF in coagulation.



Learning objectives

- Identify the role of primary and secondary hemostatic response.
- Identify the coagulation pathways.
- Summarize the causes of abnormal bleeding.
- Differentiate coagulation disorder and platelet disorders.
- Explain the pathogenesis of ITP.

Learning objectives

- Illustrate how to diagnose ITP.
- Identify main lines of treatment of ITP
- Identify functional platelet disorders.
- Enumerate the main causes of acquired platelet disorders
- Identify the inheritance of hemophilia.
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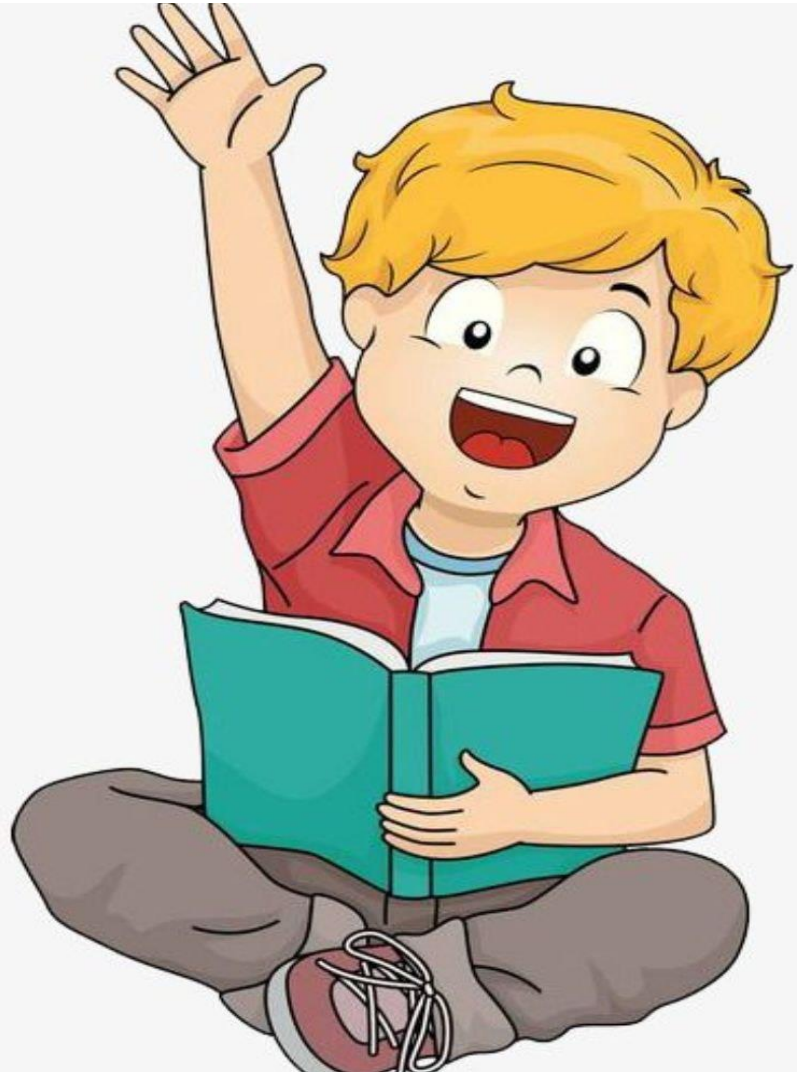
Learning objectives

- Summarize the clinical features of hemophilia.
- Explain the laboratory tests of hemophilia and their results.
- Enumerate the main lines of treatments
- Classify the types of VWD.
- Explain the laboratory results
- Summarize the main lines of treatments for VWD.
- Identify the causes of acquired coagulation disorders, pathogenesis and their main lines of treatment.

What do you know about haemostasis



Haemostasis = (Hemo+ stasis)

- refers to the process whereby blood coagulation is initiated and terminated in a tightly regulated fashion, together with the removal (or fibrinolysis) of the clot as part of vascular remodeling.

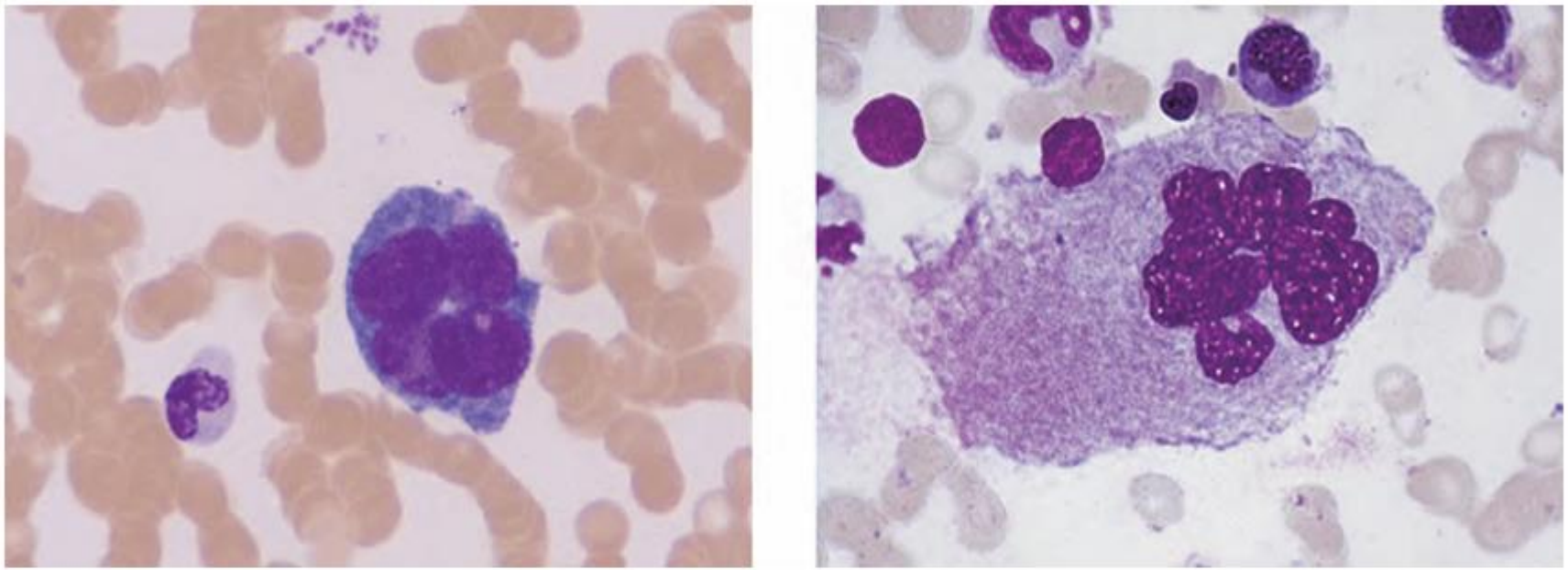
- It is essentially the global process by which vascular integrity and patency are maintained

Hemostatic response

- Vasoconstriction.(what are the benefits of vasoconstriction?)
- Platelet reactions and primary hemostatic plug formation.
- Stabilization of the platelet plug by fibrin.
- Physiological limitation of blood coagulation.

Platelets:

- Platelets are produced in the bone marrow by fragmentation of the cytoplasm of megakaryocytes, one of the largest cells in the body.
- Thrombopoietin (TPO) is the major regulator of platelet formation and 95% is produced by the liver.



(a) (b)

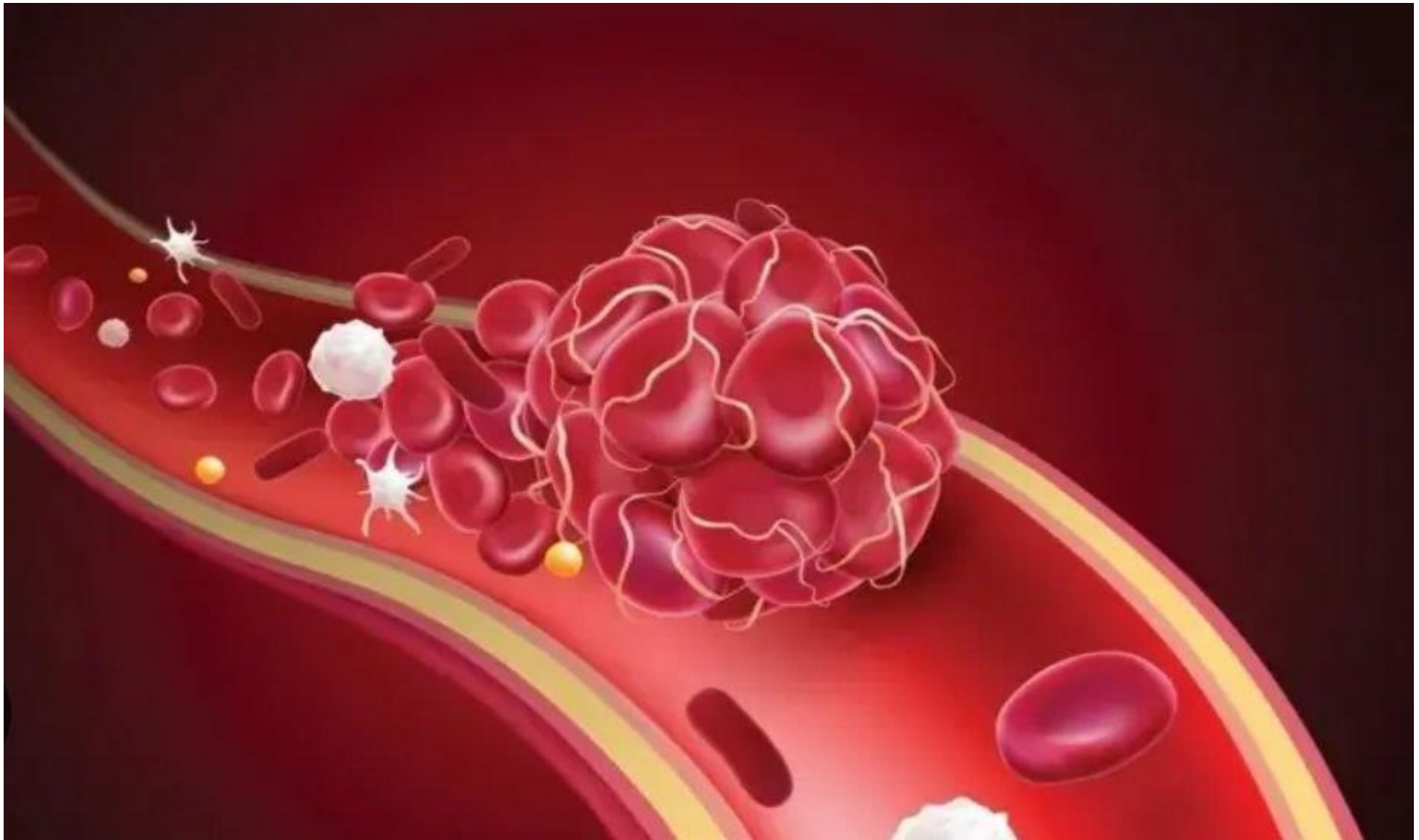
Megakaryocytes: (a) immature form with basophilic cytoplasm; (b) mature form with many nuclear lobes and pronounced granulation of the cytoplasm

- The normal platelet count is (range 150–400 × 109/L) and the normal platelet lifespan is 10 days.
- There are three major platelet functions: adhesion, aggregation and release reactions and amplification. The immobilization of platelets at the sites of vascular injury requires specific platelet–vessel wall (adhesion) and platelet–platelet (aggregation) interactions, both partly mediated through VWF

- This continuing platelet aggregation promotes the growth of the haemostatic plug, which soon covers the exposed connective tissue.

- The unstable **primary haemostatic** plug produced by these platelet reactions in the first minute or so following injury is usually sufficient to provide temporary control of bleeding.

Blood coagulation(2nd hemostatic response)



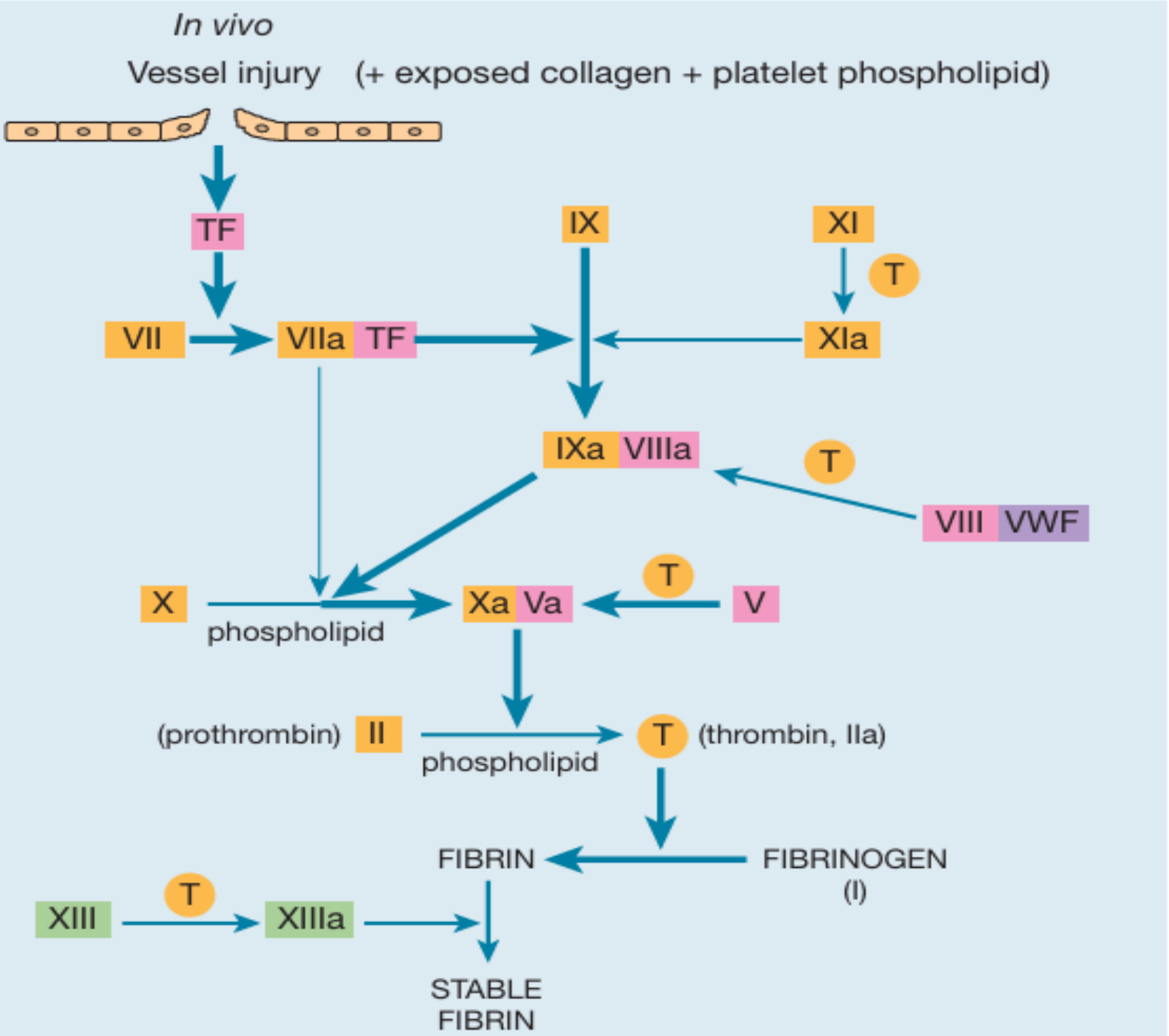
Coagulation cascade

- Thrombin generation is dependent on:
- three enzyme complexes, each consisting of **protease, cofactor, phospholipids (PL) and calcium**.
- They are: (i) extrinsic Xase (VIIa, TF, PL, Ca2+) generating FXa;
- (ii) intrinsic Xase (IXa, VIIIa, PL, Ca2+) also generating FXa;
- (iii) prothrombinase complex (Xa, Va, PL, Ca2+) generating thrombin.

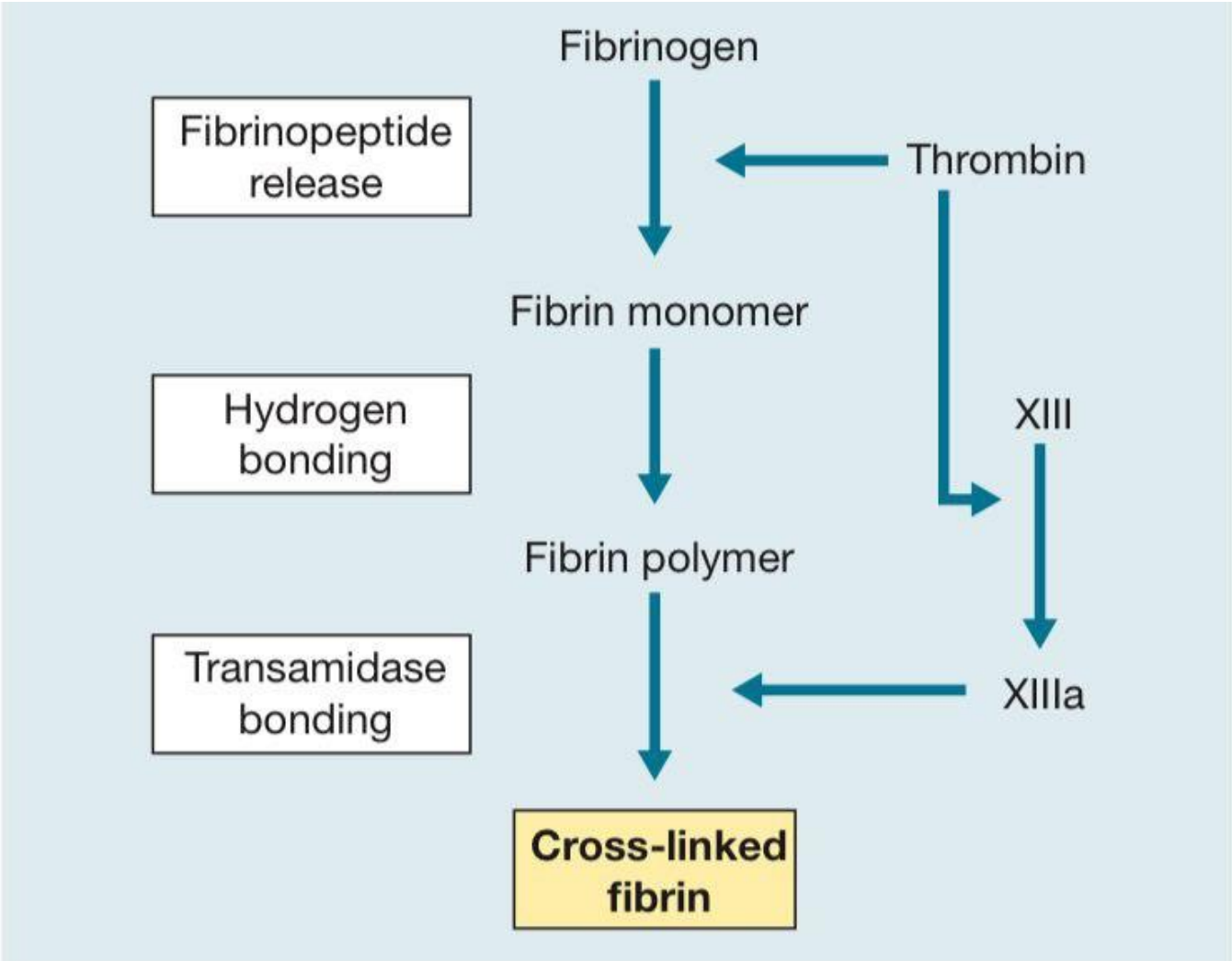
Coagulation factors

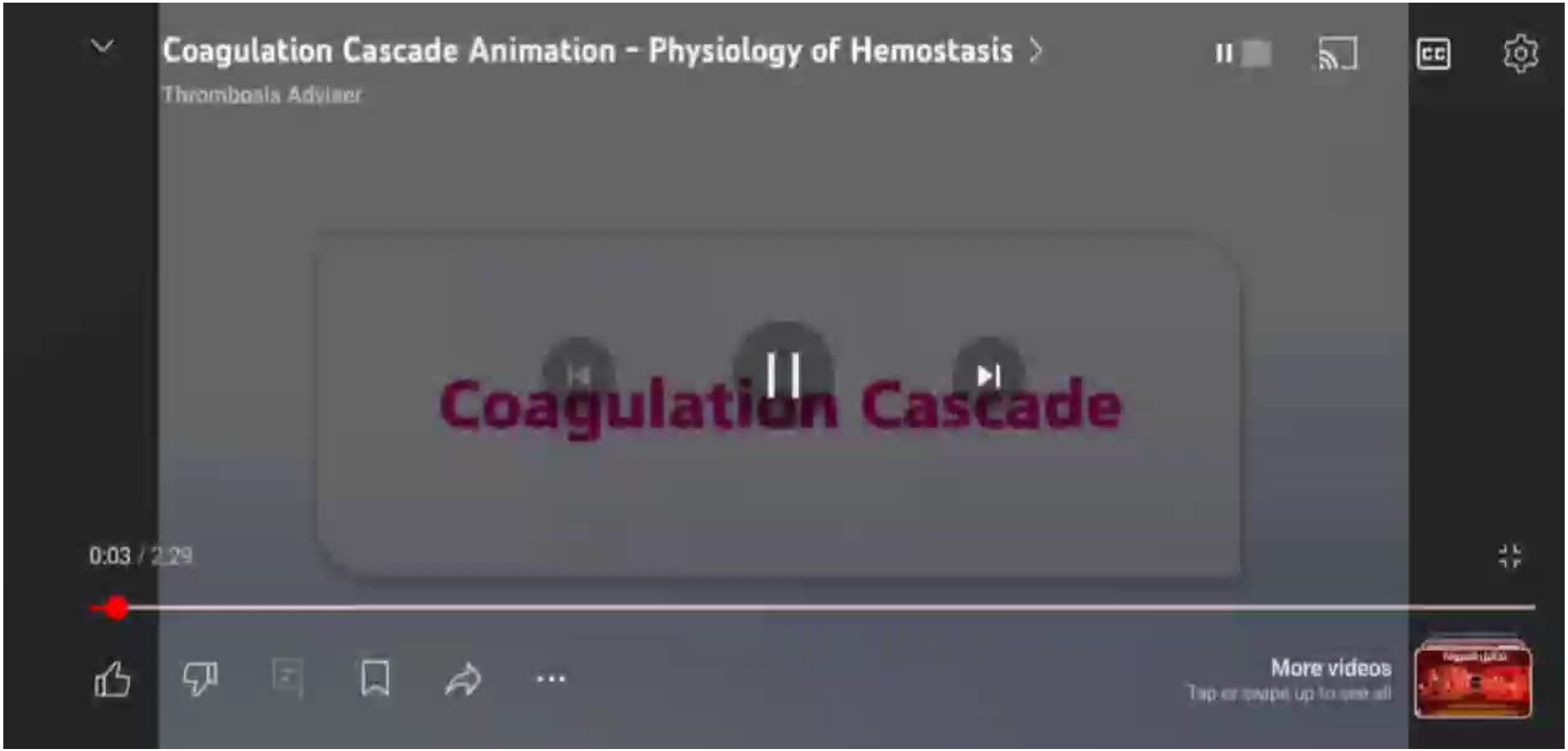
Factor number	Descriptive name	Active form
I	Fibrinogen	Fibrin subunit
II	Prothrombin	Serine protease
III	Tissue factor	Receptor/cofactor*
V	Labile factor	Cofactor
VII	Proconvertin	Serine protease
VIII	Antihaemophilic factor	Cofactor
IX	Christmas factor	Serine protease
X	Stuart–Prower factor	Serine protease
XI	Plasma thromboplastin antecedent	Serine protease
XII	Hageman (contact) factor	Serine protease
XIII	Fibrin-stabilizing factor	Transglutaminase
	Prekallikrein (Fletcher factor)	Serine protease
	HMWK (Fitzgerald factor)	Cofactor*

HMWK, high molecular weight kininogen.
* Active without proteolytic modification.



The pathway of blood coagulation in vivo initiated by tissue factor (TF) on the cell surface. When plasma comes into contact with TF, factor VII binds to TF. The complex of TF and activated VII (VIIa) activates X and IX. The generation of thrombin from prothrombin by the action of Xa–Va complex leads to fibrin formation. Importantly, the small amounts of thrombin generated serve to greatly amplify coagulation. Thrombin activates XI, VIII, V and XIII, and also cleaves VIII from its carrier von Willebrand factor (VWF), massively increasing the formation of VIIIa–IXa and hence of Xa–Va.


Fibrinogen
Fibrinopeptide release
Thrombin
Fibrin monomer
Hydrogen bonding
XIII
Fibrin polymer
Transamidase bonding
XIIIa
Cross-linked fibrin

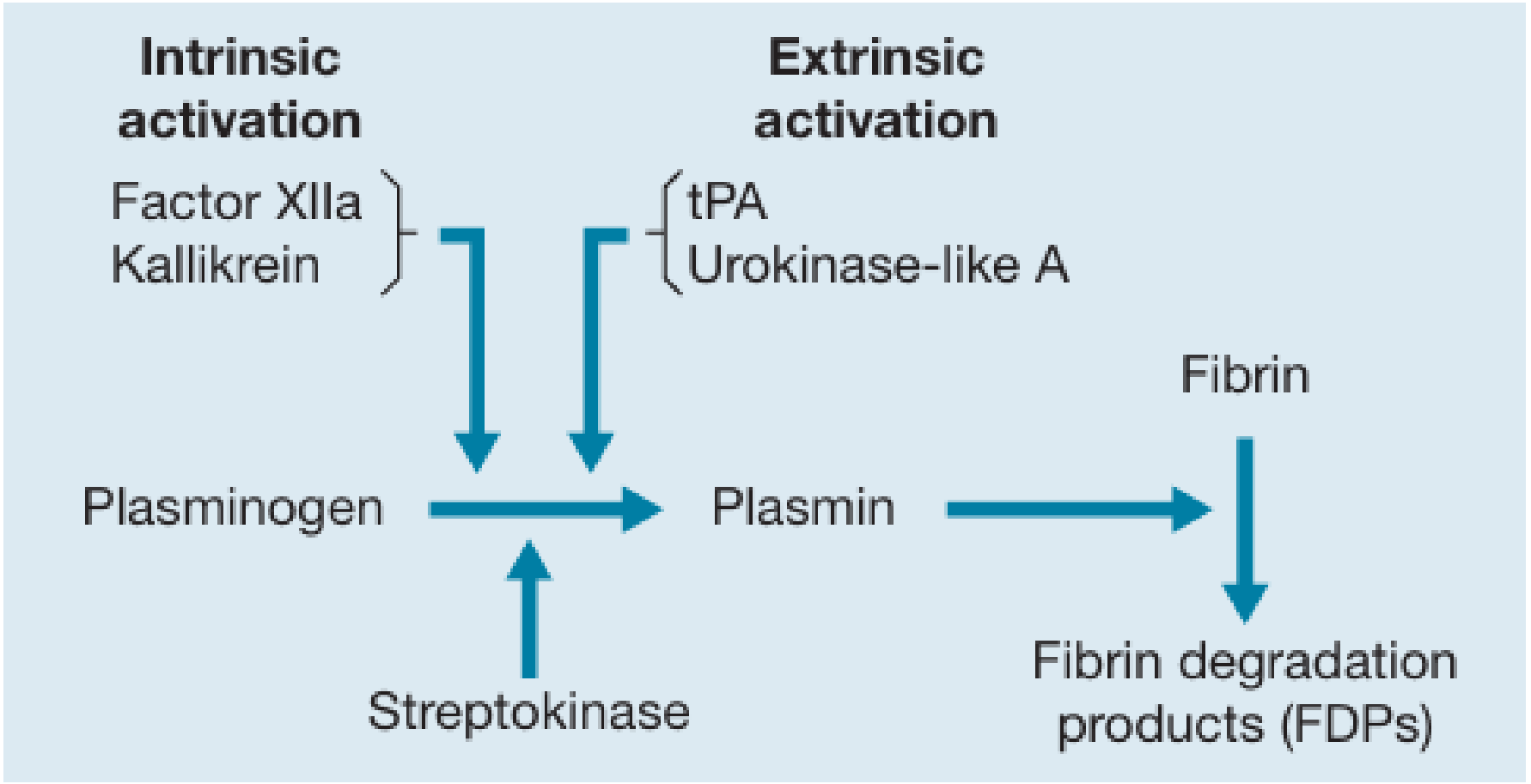

Coagulation Cascade Animation - Physiology of Hemostasis
Thrombosis Adviser
Coagulation Cascade
0:03 / 2:29
More videos

Fibrinolysis

- The final step in the regulation of fibrin deposition is the prevention and/or rapid removal of insoluble fibrin by the fibrinolytic system

- Once sufficient fibrin is generated, it binds tissue plasminogen activator (**tPA**), leading to the increased activation of plasminogen (**PLG**).

- This results in the formation of plasmin at the site of the fibrin clot, which breaks down fibrin into soluble fibrin degradation products


Intrinsic activation
Extrinsic activation
Factor XIIa
Kallikrein
tPA
Urokinase-like A
Fibrin
Plasminogen
Plasmin
Streptokinase
Fibrin degradation products (FDPs)

Naturally occurring inhibitors of coagulation

- The protein C pathway (inhibit cofactor V and VIII)
- Antithrombin
- Heparin
- TFPI (tissue factor pathway inhibitor)
- HCII (heparin cofactor II)

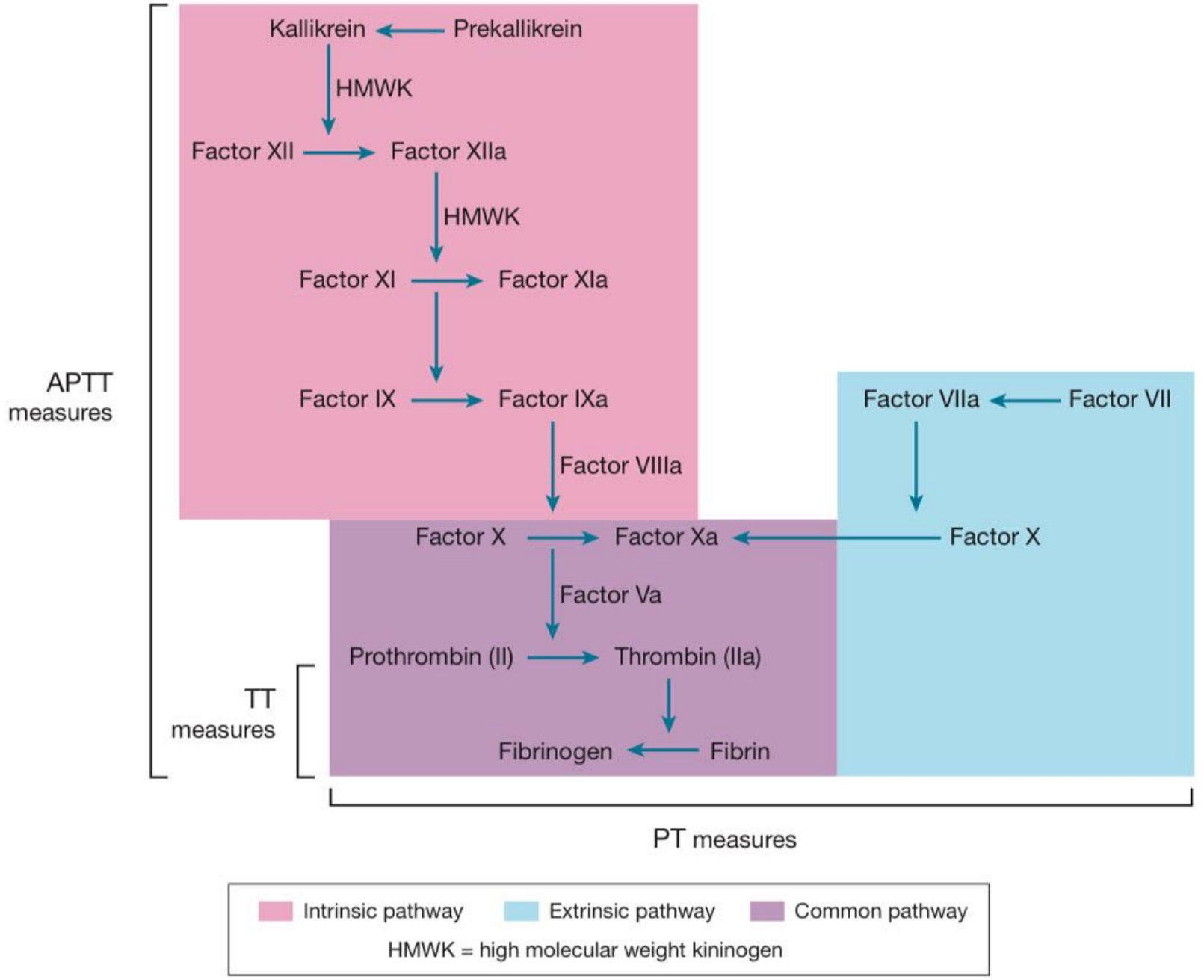
Screening tests of blood coagulation

- Screening tests provide an assessment of the ‘extrinsic’ and ‘intrinsic’ systems of blood coagulation and also the central conversion of fibrinogen to fibrin

Table 24.3 Screening tests used in the diagnosis of coagulation disorders (see also Fig. 24.10)

Screening tests	Abnormalities indicated by prolongation	Most common cause of coagulation disorder
Thrombin time (TT)	Deficiency or abnormality of fibrinogen or inhibition of thrombin by heparin or FDPs	DIC Heparin therapy
Prothrombin time (PT)	Deficiency or inhibition of one or more of the following coagulation factors: VII, X, V, II, fibrinogen	Liver disease Warfarin therapy DIC
Activated partial thromboplastin time (APTT or PTTK)	Deficiency or inhibition of one or more of the following coagulation factors: XII, XI, IX (Christmas disease), VIII (haemophilia), X, V, II, fibrinogen	Haemophilia, Christmas disease (+ conditions above)
Fibrinogen quantitation	Fibrinogen deficiency	DIC, liver disease

DIC, disseminated intravascular coagulation; FDPs, fibrin degradation products.
N.B. Platelet count and the tests of platelet function are also used in screening patients with a bleeding disorder (p. XXX).


Kallikrein
Prekallikrein
HMWK
Factor XII
Factor XIIa
HMWK
Factor XI
Factor XIa
Factor IX
Factor IXa
Factor VIIIa
Factor VIIa
Factor VII
Factor X
Factor Xa
Factor X
Factor Va
Prothrombin (II)
Thrombin (IIa)
Fibrinogen
Fibrin
APTT measures
TT measures
PT measures
Intrinsic pathway
Extrinsic pathway
Common pathway
HMWK = high molecular weight kininogen

- The prothrombin time (PT) measures factors VII, X, V, prothrombin and fibrinogen.
- The normal time for clotting is 10–14 s. It may be expressed as the international normalized ratio (INR)

- The activated partial thromboplastin time (APTT) measures factors **VIII, IX, XI** and **XII** in addition to factors X, V, prothrombin and fibrinogen.
- The normal time for clotting is approximately 30–40 s.

- The thrombin (clotting) time (TT) is sensitive to a deficiency of fibrinogen or inhibition of thrombin.
- Diluted bovine thrombin is added to citrated plasma at a concentration giving a clotting time of 14–16 s with normal subjects

Bleeding time:

- The bleeding time is not a reliable assessment of platelet function as it is insensitive and has poor reproducibility.
- It was used to identify abnormal platelet function, including the diagnosis of VWF deficiency, but is no longer used in routine clinical practice.

Tests of platelet function

- Conventional **platelet aggregometry** measures the fall in light absorbance in platelet-rich plasma as platelets aggregate
- The five external aggregating agents most commonly used are ADP, collagen, ristocetin, arachidonic acid and adrenaline.
- The pattern of response to each agent helps to make the diagnosis.
- Flow cytometry is now increasingly used in routine practice to identify platelet glycoprotein defects.
- **PFA-100.**

Abnormal bleeding :

Bleeding disorders may result from:

- 1 Vascular disorders.
- 2 Thrombocytopenia.
- 3 Defective platelet function.
- 4 Defective coagulation.

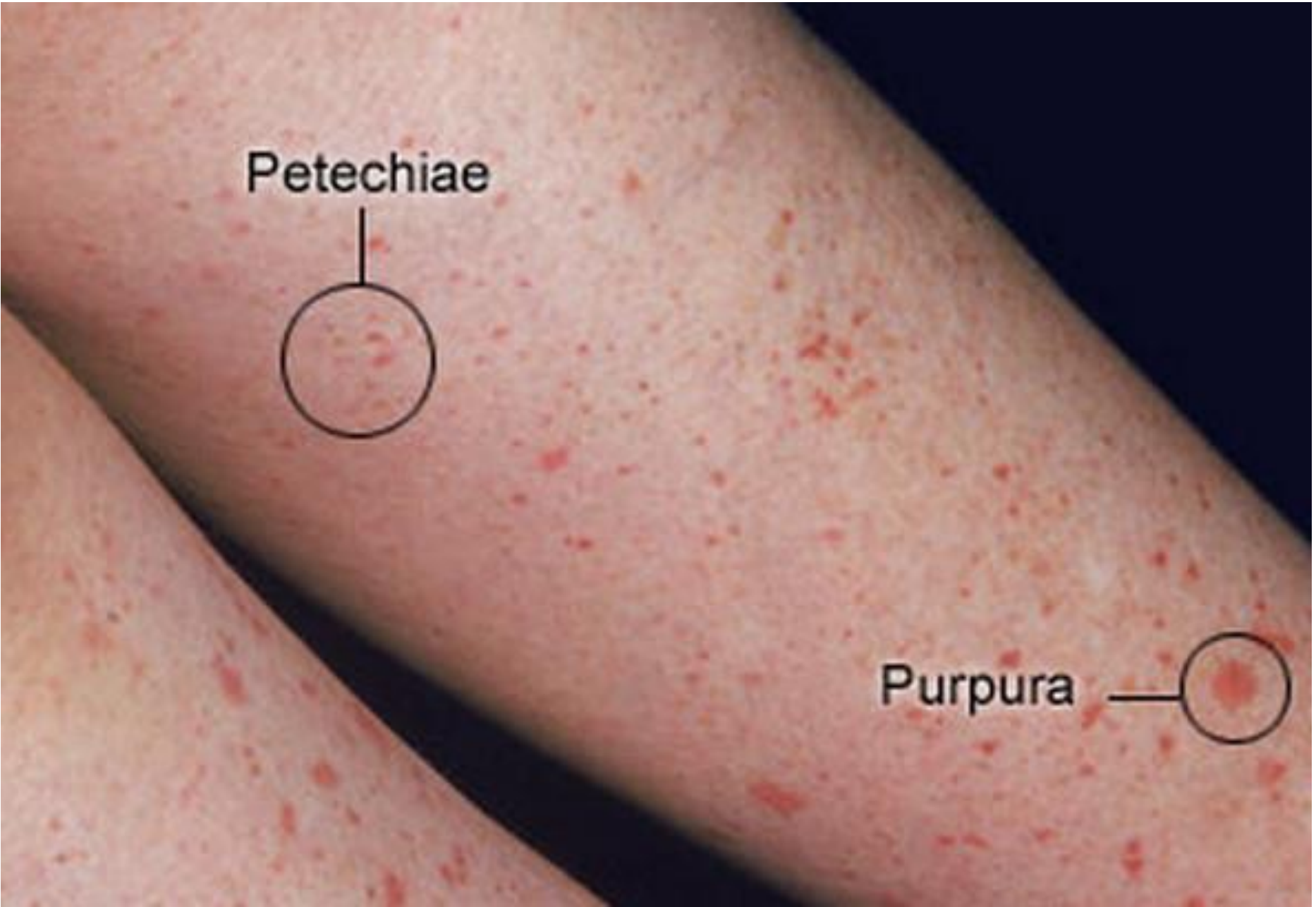
Bleeding disorders caused by vascular and platelet abnormalities …

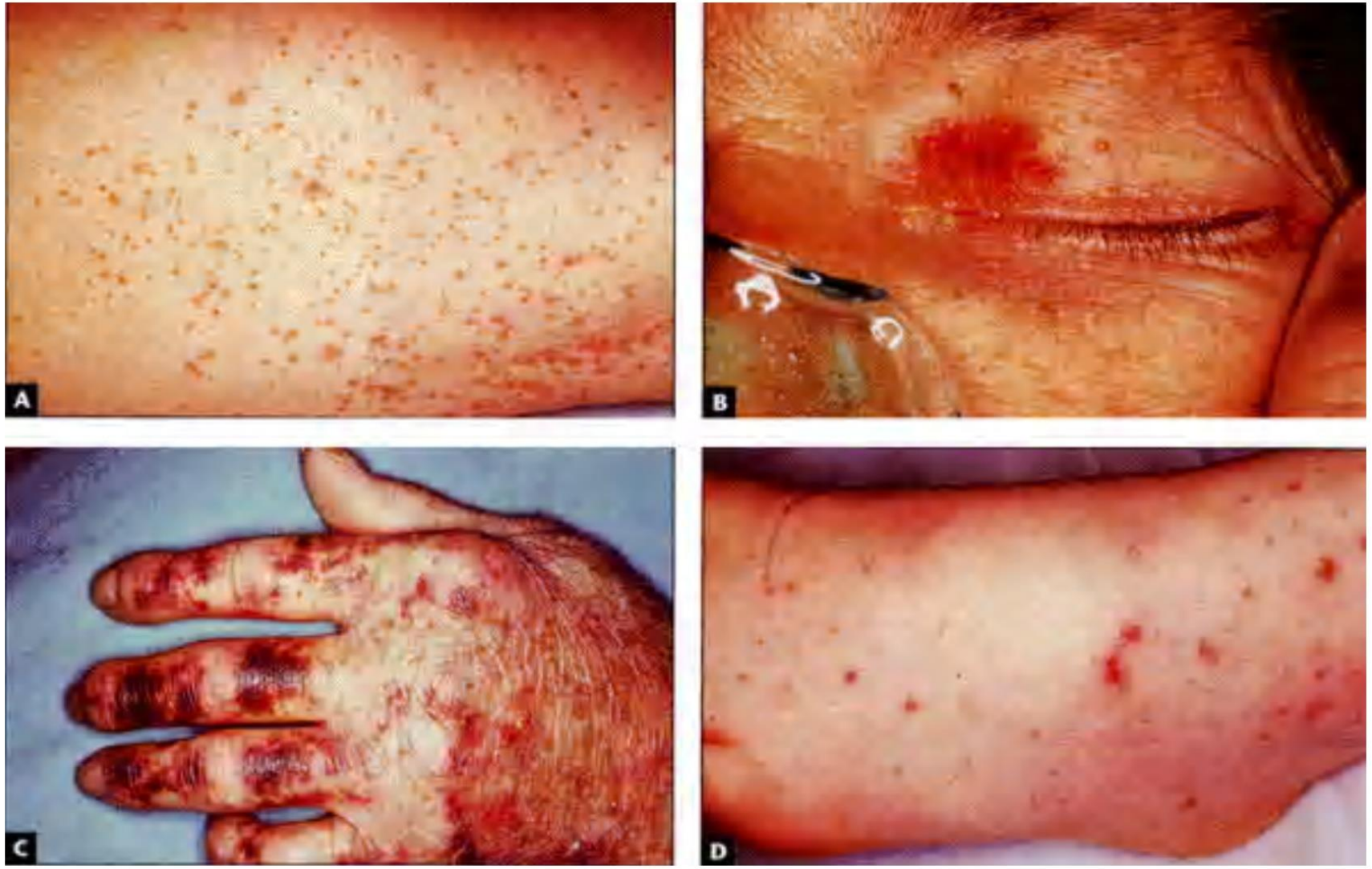
Table 25.1 Clinical differences between diseases of platelets/vessel wall or of coagulation factors.

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

Inherited vascular disorders

- Most often, they induce small hemorrhages (petechiae and purpura) in the skin or mucous membranes, particularly the gingiva.
- **The platelet count, bleeding time,PFA-100 test, and results of the coagulation tests (PT, PTT) are usually normal**


Petechiae
Purpura



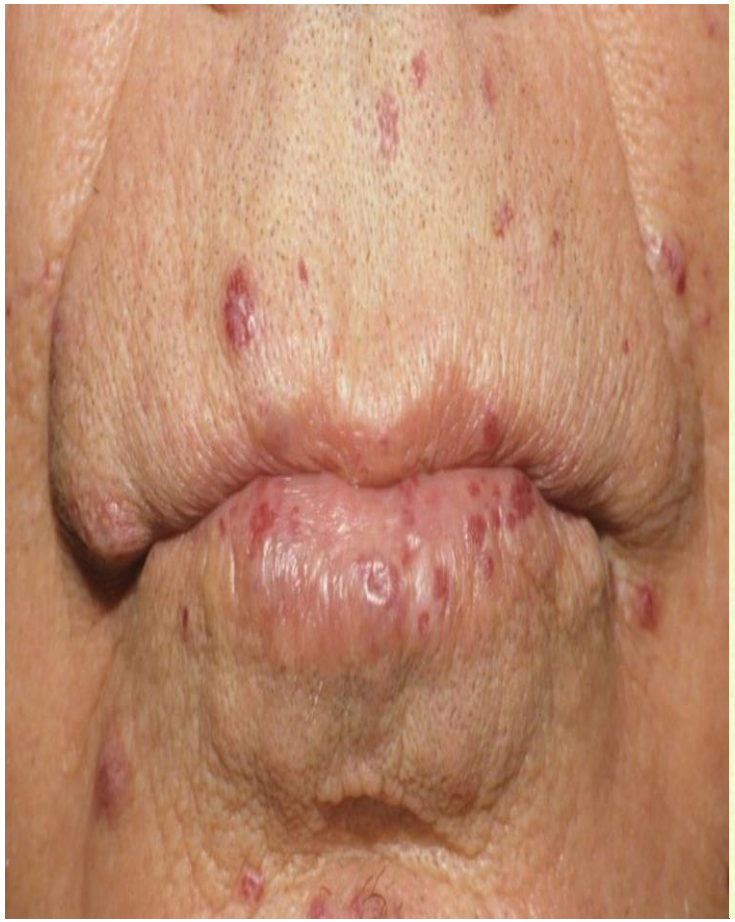
Bleeding disorders caused by vessel wall abnormality

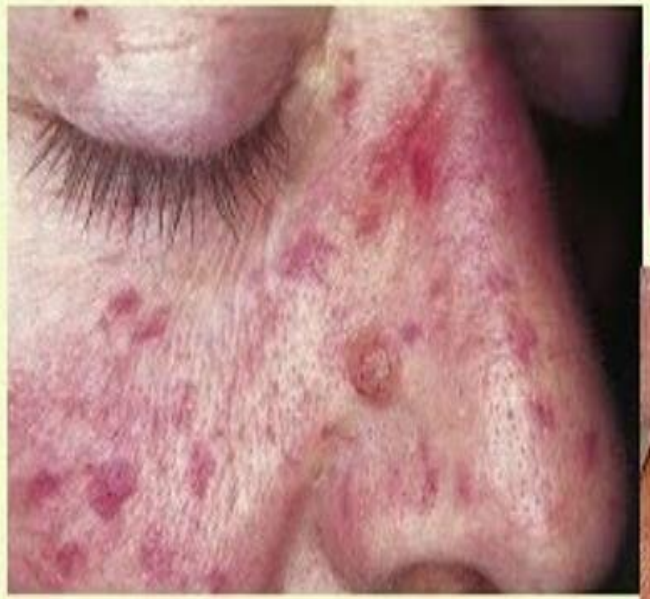
They induce small hemorrhages (petechiae and purpura) in the skin or mucous membranes, particularly the gingivae.

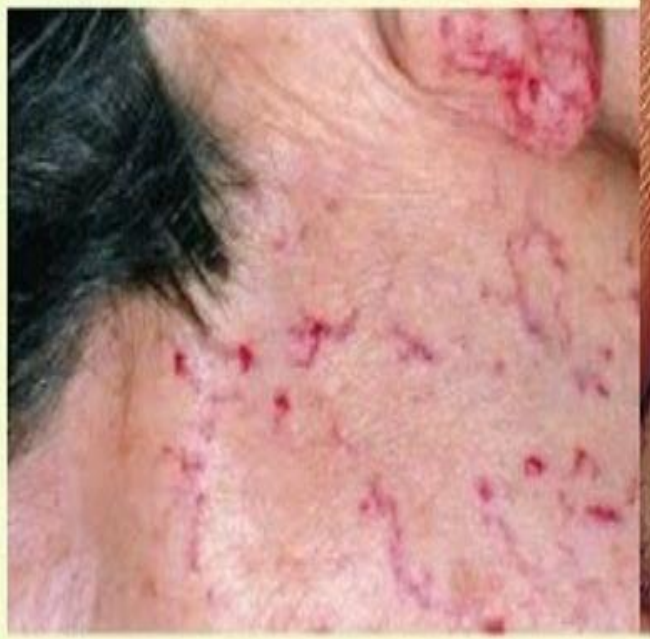
Hereditary hemorrhagic telangiectasia:

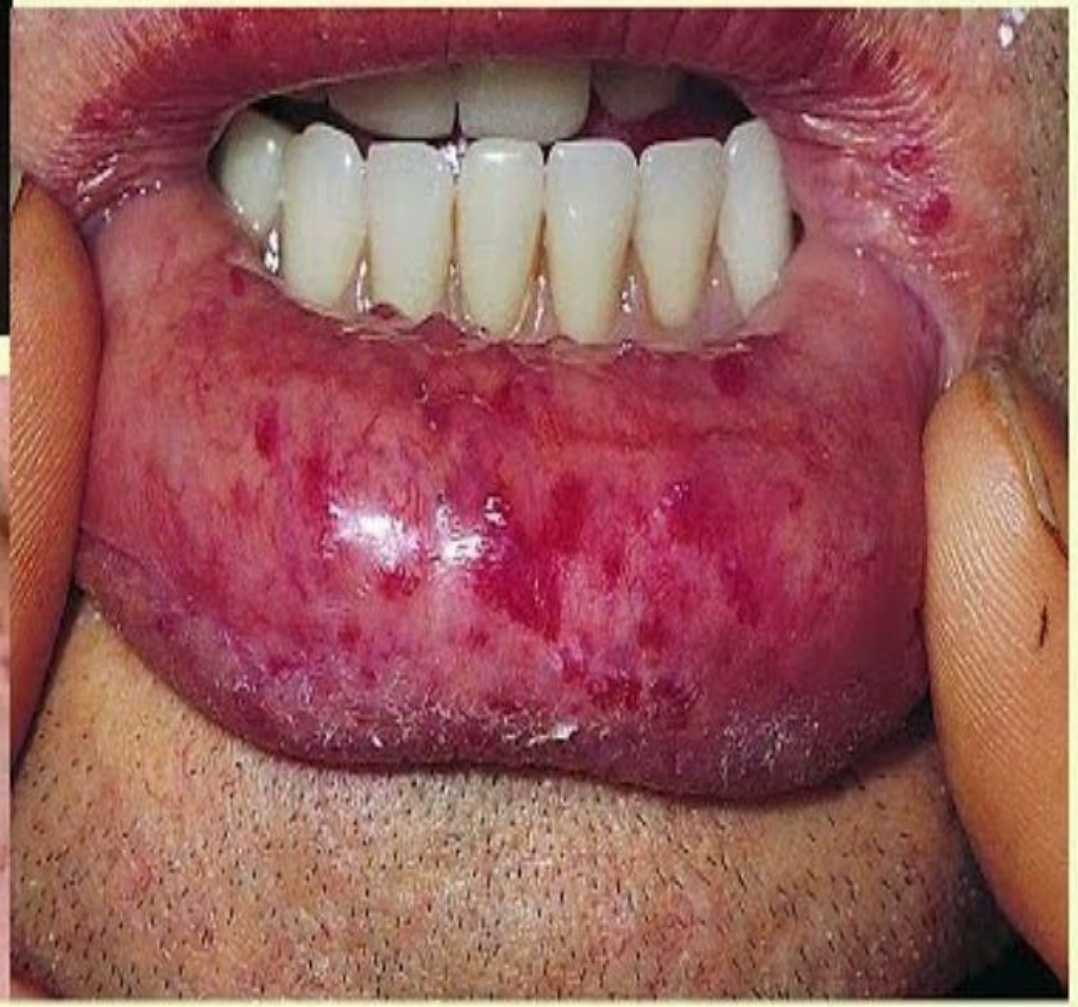
- This uncommon disease is transmitted as an autosomal dominant trait
- Caused by mutations of the endothelial protein, endoglin.
- There are dilated microvascular swellings which appear during childhood and become more numerous in adult life.

Hereditary hemorrhagic telangiectasia









Acquired vascular disorders

- **S**imple easy bruising.
- **S**enile purpura.
- **S**teroids.
- **S**curvey.

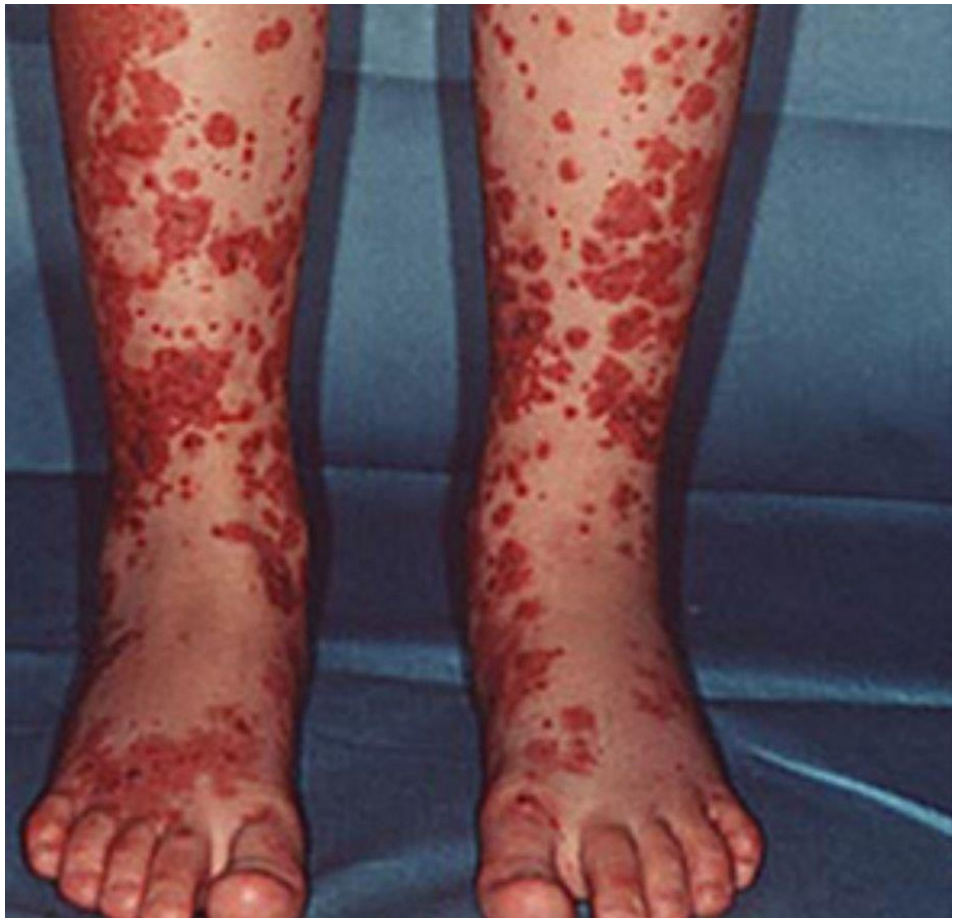
- **D**rugs. the vascular injury is mediated by **drug-induced antibodies** and deposition of **immune complexes** in the vessel walls, leading to hypersensitivity (leukocytoclastic) vasculitis.

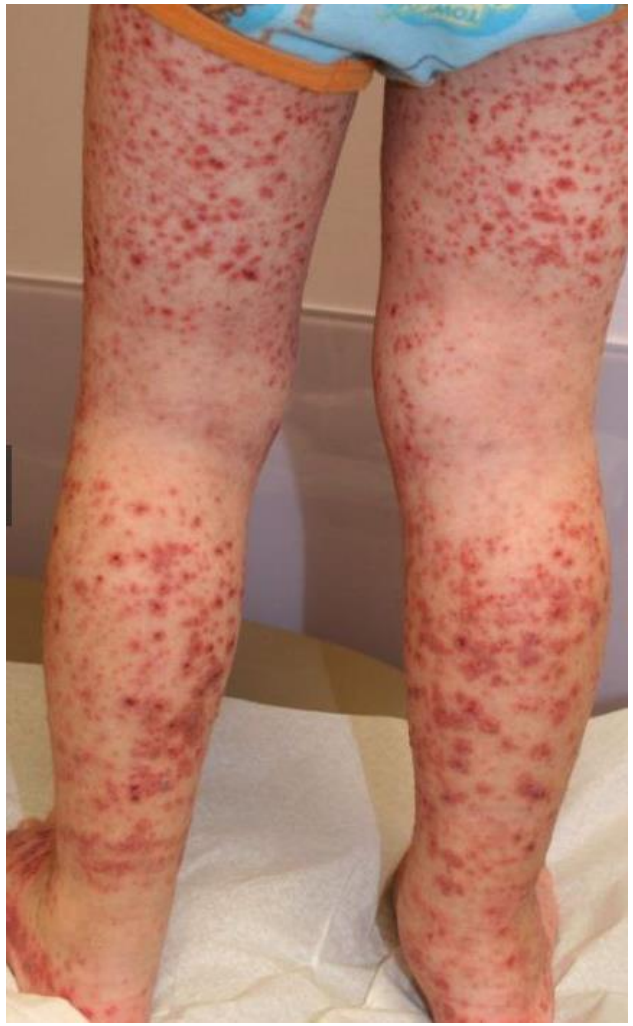
- **I**nfection. The involved mechanism is presumably **microbial damage** to the microvasculature **(vasculitis)** or **disseminated intravascular coagulation (DIC)**.

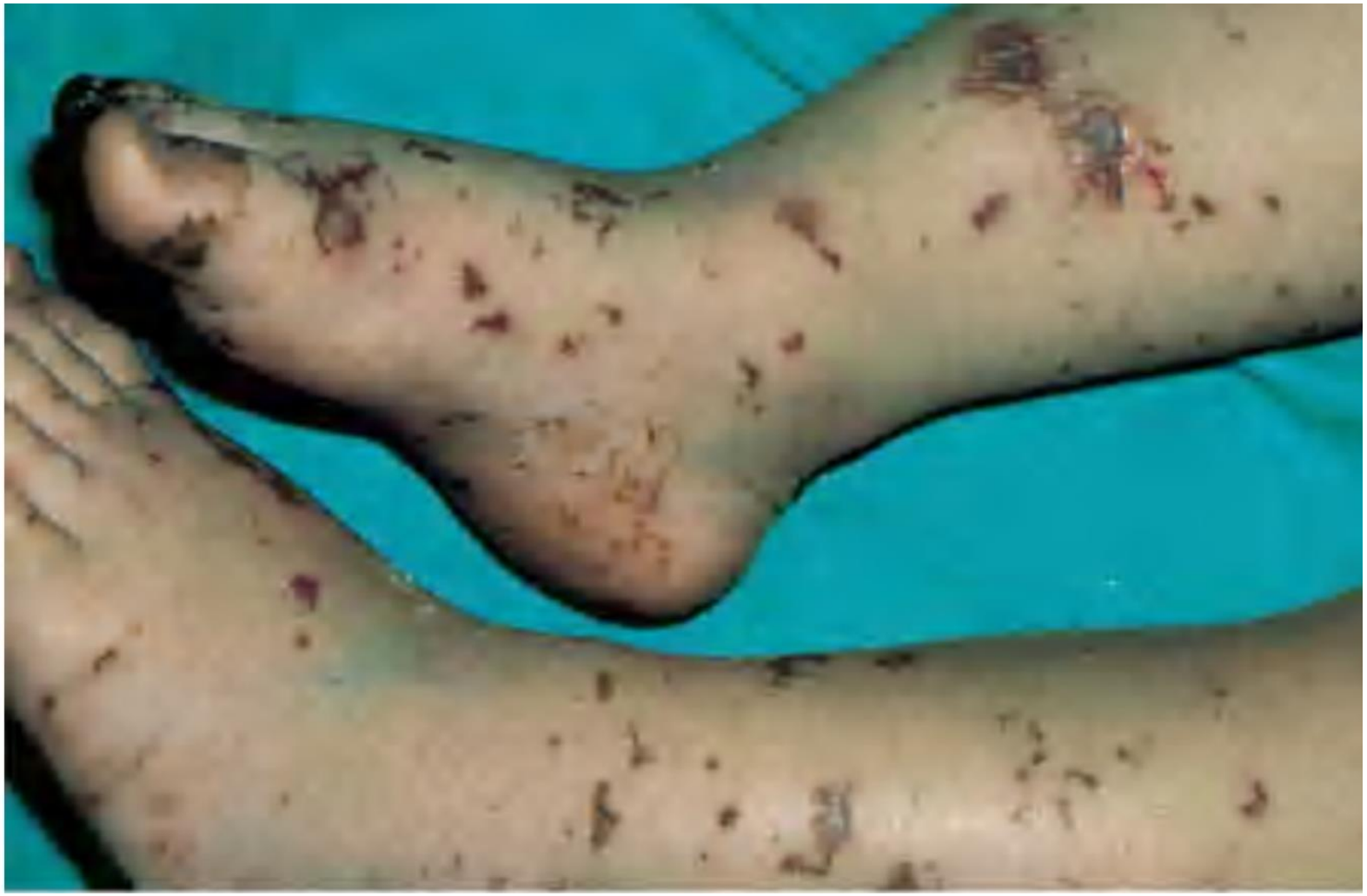
- The Henoch–Schönlein syndrome is usually seen in children and often follows an acute upper respiratory tract infection. It is an IgA-mediated vasculitis.

- The characteristic purpuric rash accompanied by localized oedema and itching is usually most prominent on the buttocks and extensor surfaces of the lower legs and elbows

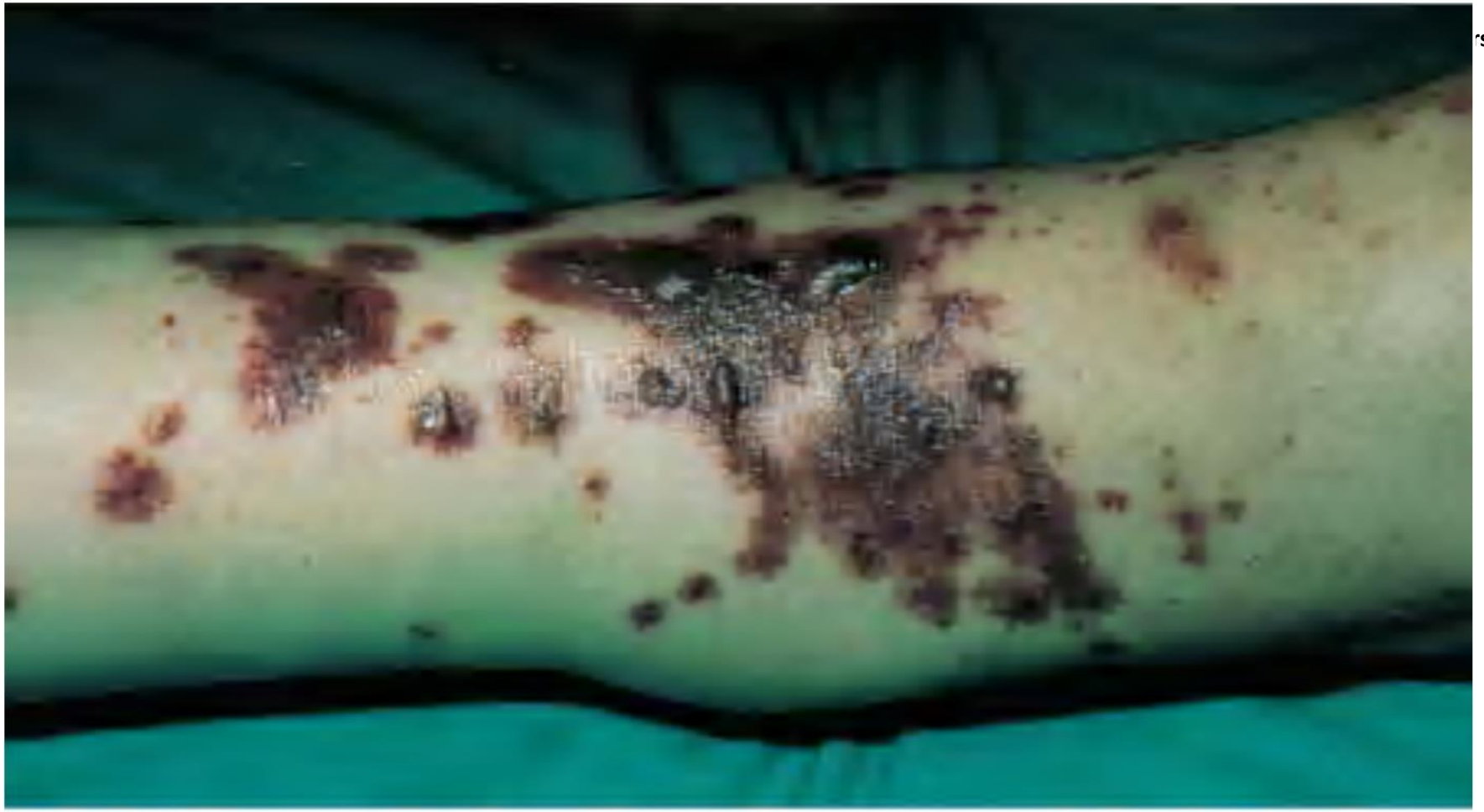
Henoch–Schönlein purpura



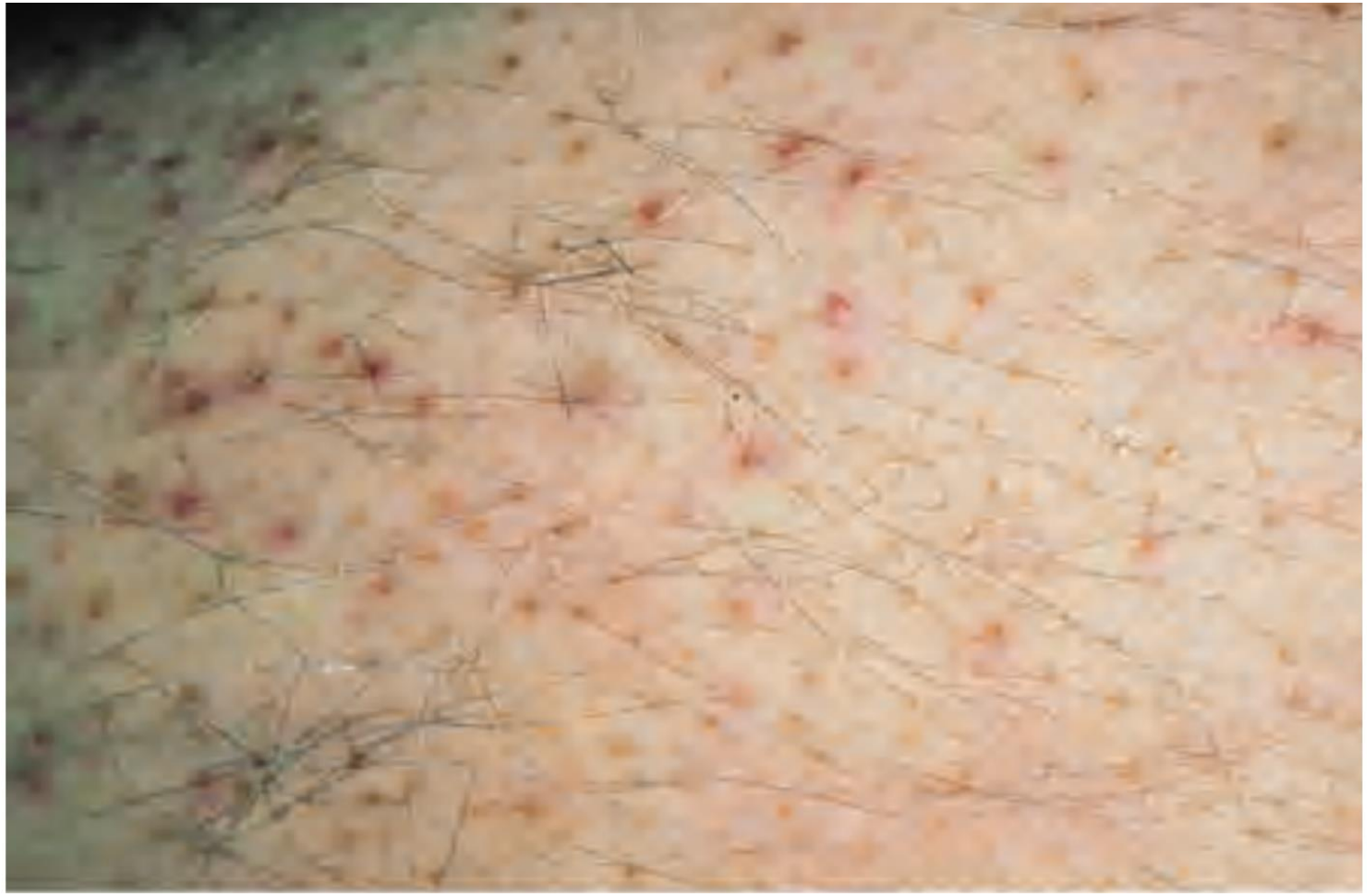




Meningococcemia, stellate purpura

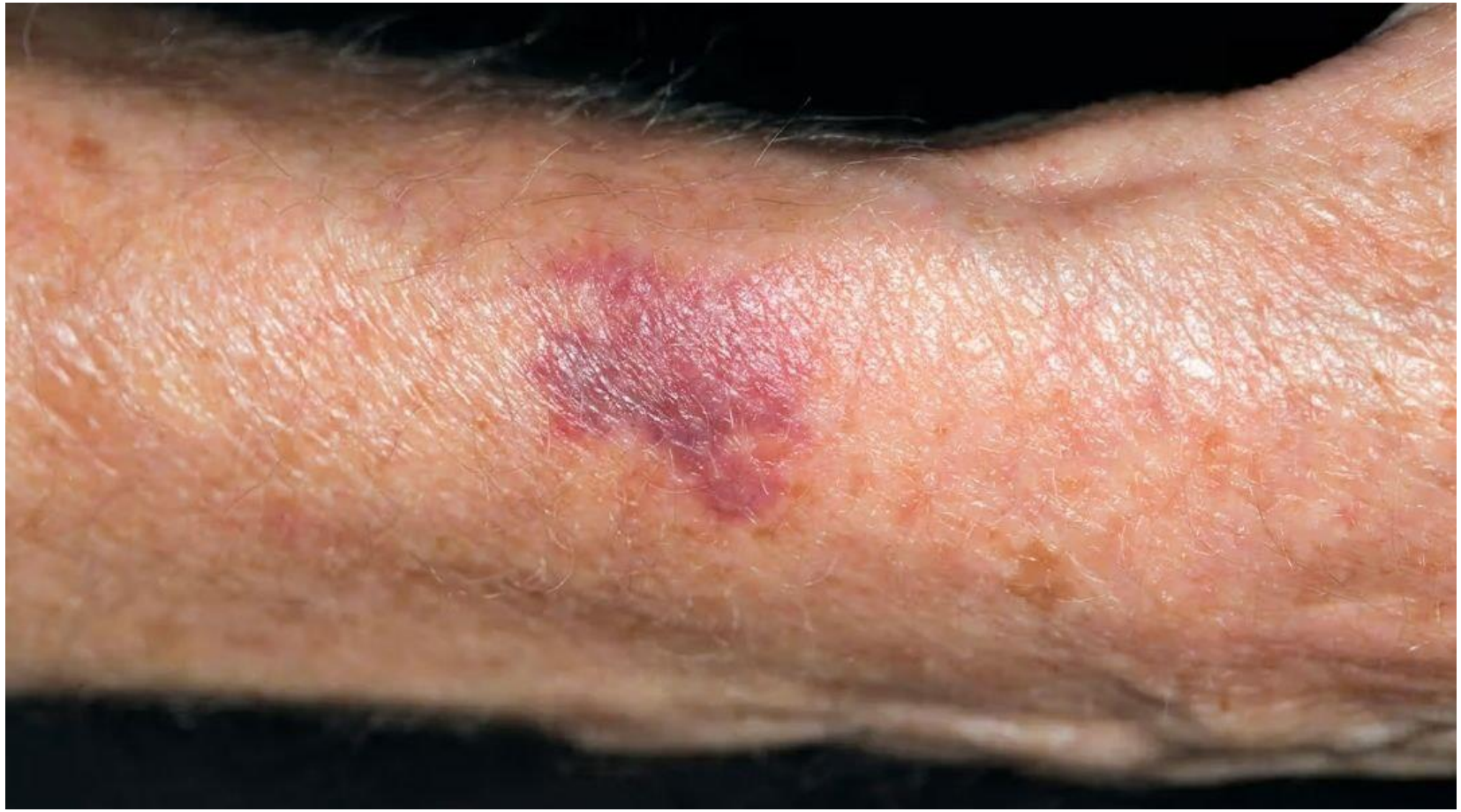


Leukocytoclastic vasculitis secondary to furosemide.



Scurvy: Vitamin C deficiency: Note parafollicular petechiae

The involved mechanism is impaired formation of collagens needed for support of vessel walls.



Senile purpura caused by atrophy of the supporting tissues of cutaneous blood vessels is seen mainly on dorsal aspects of the forearms and hands

Q/A 76 year old female notices that small, pinpoint areas of superficial hemorrhage have appeared on her gums and on the skin of her arms and legs over several weeks.
She is found to have a normal (PT) and (PTT).
Her CBC shows a [Hb] of 12.7 g/dL, platelet count of 260,000/µL, and WBC count of 8600/µL. Her template bleeding time is 3 minutes, and PFA-100 test was normal. Which o the following conditions best explains these findings?

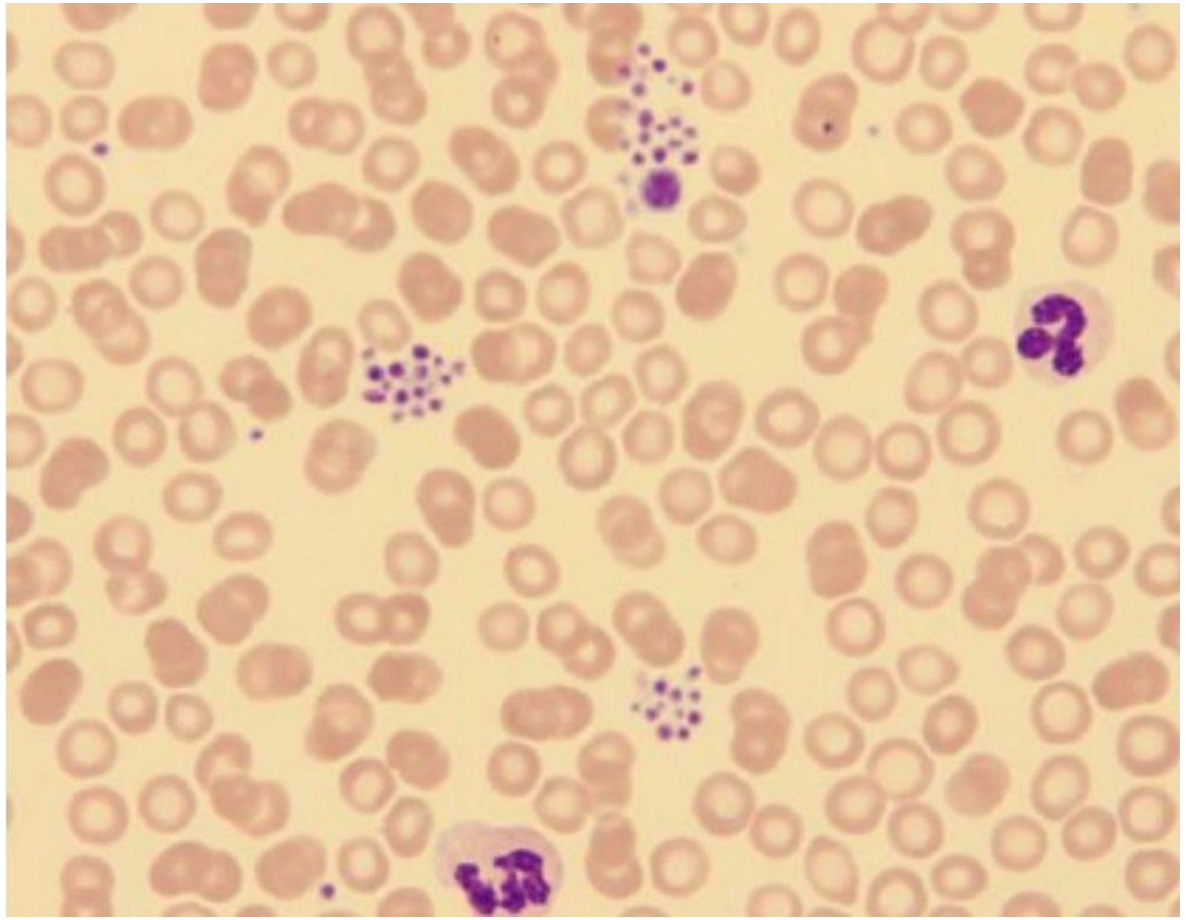
a. Macronodular cirrhosis.
b. Chronic renal failure.
c. Meningococcemia.
d. Metastatic carcinoma.
e. Vitamin C deficiency.

Thrombocytopenia:

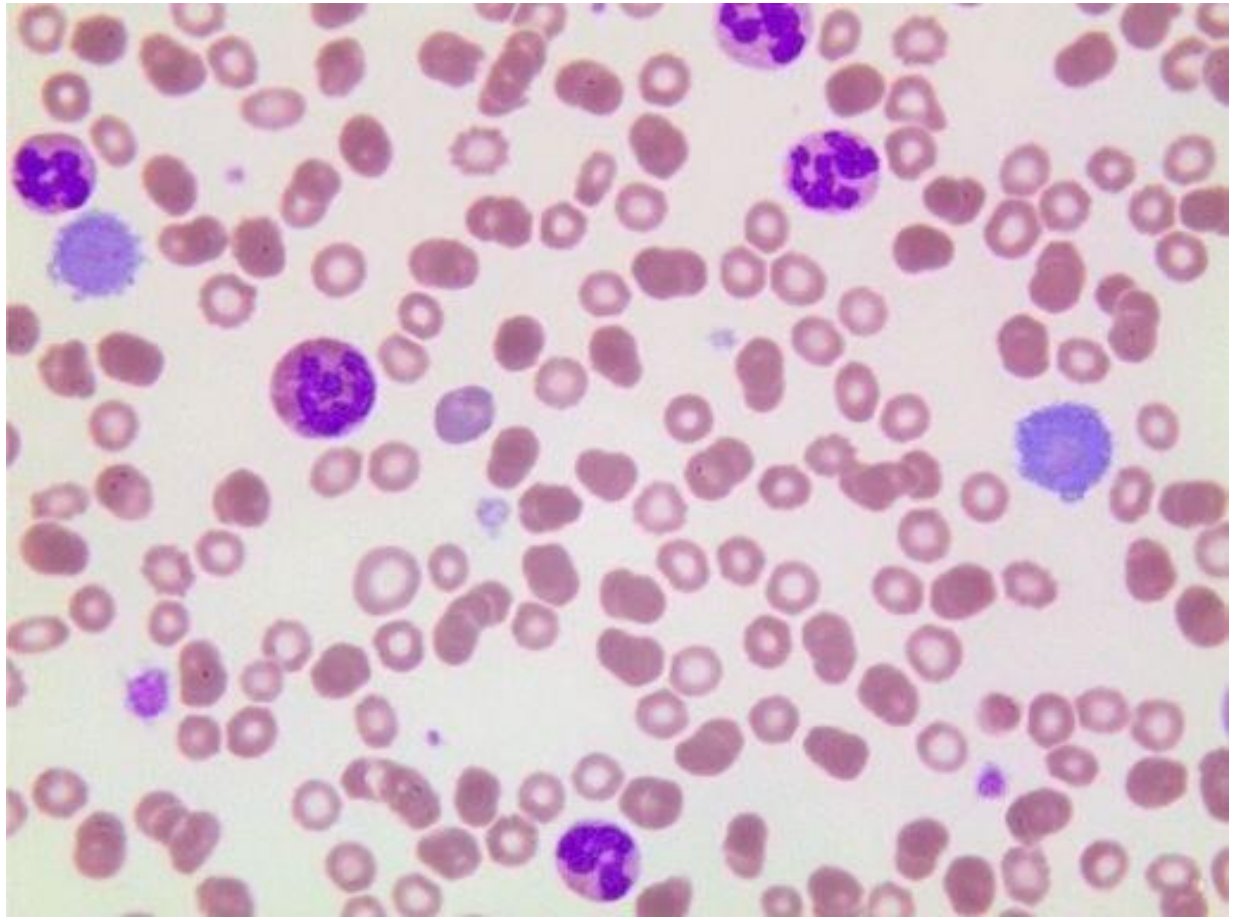
- **Pseudo-thrombocytopenia.**
- **Giant platelets**
- **Platelet aggregate**

- **True thrombocytopenia**

Left: platelet aggregates



Right: giant platelets



Thrombocytopenia:

- Failure of platelet production.
- Increased destruction of platelets.
- Abnormal distribution of platelets.
- Dilutional loss.

A count **below 100,000** platelets/µL is generally considered to constitute thrombocytopenia.

However, **spontaneous bleeding** does not become evident until platelet counts fall **below 20,000** platelets/µL.

Platelet counts in the range of **20,000 to 50,000** platelets/µL can aggravate post-traumatic bleeding.

Bleeding resulting from thrombocytopenia is associated with a **normal** PT and PTT .

Spontaneous bleeding associated with thrombocytopenia most often involves small vessels

What are the results of screening laboratory tests in bleeding due to thrombocytopenia?

- Platelet count is reduced.
- A prolonged bleeding time, abnormal PFA-100 test.
- A normal PT and PTT.

Failure of platelets products

- This is the **most common** cause of thrombocytopenia and is usually part of a generalized bone marrow failure.
- Selective megakaryocyte depression may result from drug toxicity or viral infection.
- **Rarely** it is **congenital** as a result of mutation of the c-MPL thrombopoietin receptor or of the RBM8A gene in association with absent radii.

• Failure of platelet production:

Failure of platelet production
Selective megakaryocyte depression
- rare congenital defects (see text)
- drugs, chemicals, viral infections

Part of general bone marrow failure
- cytotoxic drugs
- radiotherapy
- aplastic anaemia
- leukaemia
- myelodysplastic syndromes
- myelofibrosis
- marrow infiltration (e.g. carcinoma, lymphoma, Gaucher's disease)
- multiple myeloma
- megaloblastic anaemia
- HIV infection

Increased consumption of platelets

- Immune
- autoimmune
- idiopathic
- associated with systemic lupus erythematosus, chronic
- lymphocytic leukemia or lymphoma;
- infections: Helicobacter pylori, HIV, other viruses, malaria
- drug-induced, e.g. heparin
- post-transfusional purpura
- fetomaternal alloimmune thrombocytopenia
- Disseminated intravascular coagulation
- Thrombotic thrombocytopenic purpura

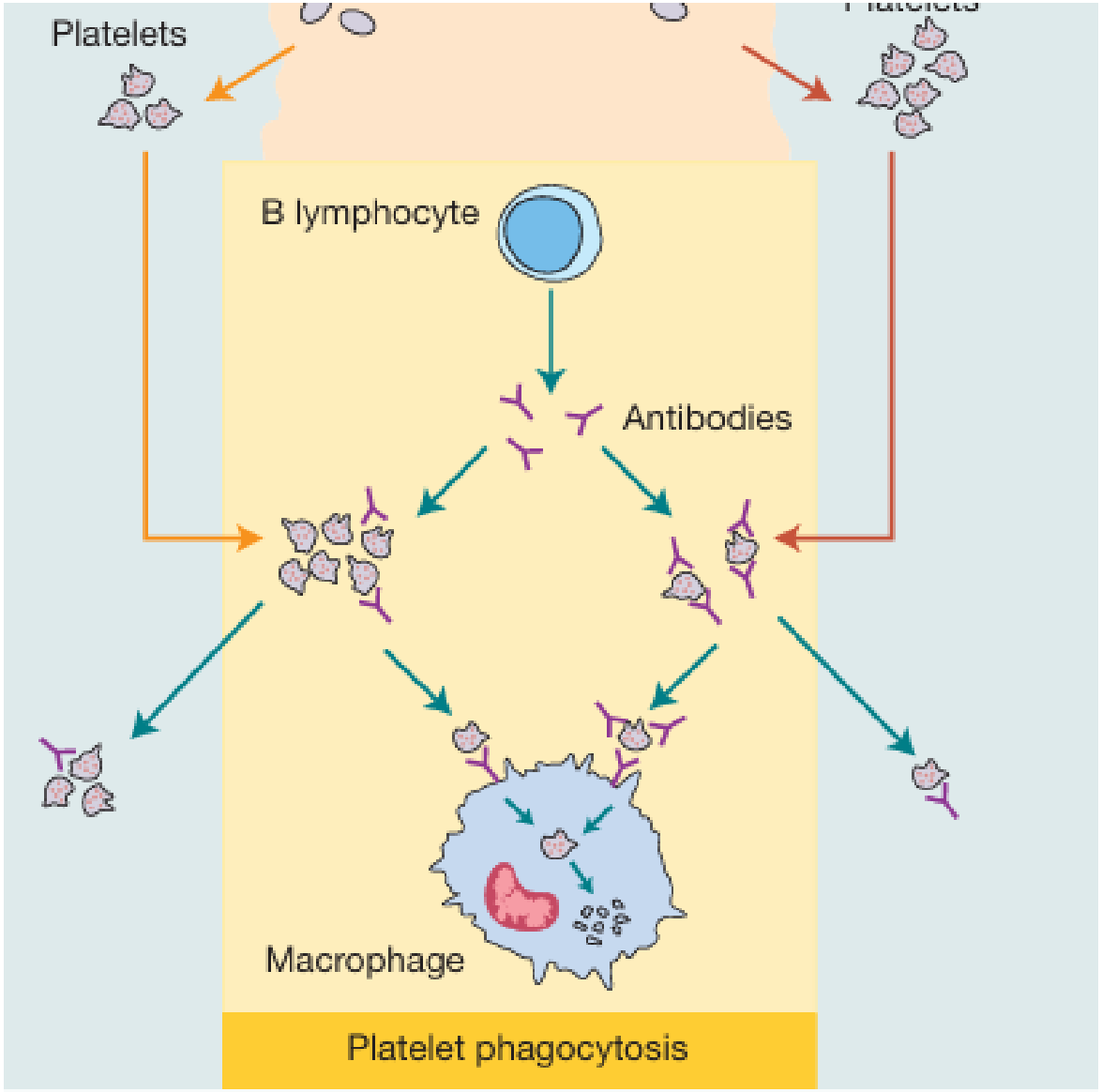
Autoimmune (idiopathic) thrombocytopenic purpura

- **Chronic idiopathic thrombocytopenic purpura (ITP)**
- This is a relatively common disorder. The highest incidence has been considered to be in women aged 15–50 years, It is the most common cause of thrombocytopenia without anemia or neutropenia.

Pathogenesis:

- Platelet **autoantibodies**, usually IgG, result in the **premature removal** of platelets from the circulation by **macrophages** of the reticuloendothelial system, especially the spleen.
- In many cases, the antibody is directed against the glycoprotein (GP) on the surface of platelets.
- Opsonized platelets are susceptible for phagocytosis.

ITP pathogenesis:

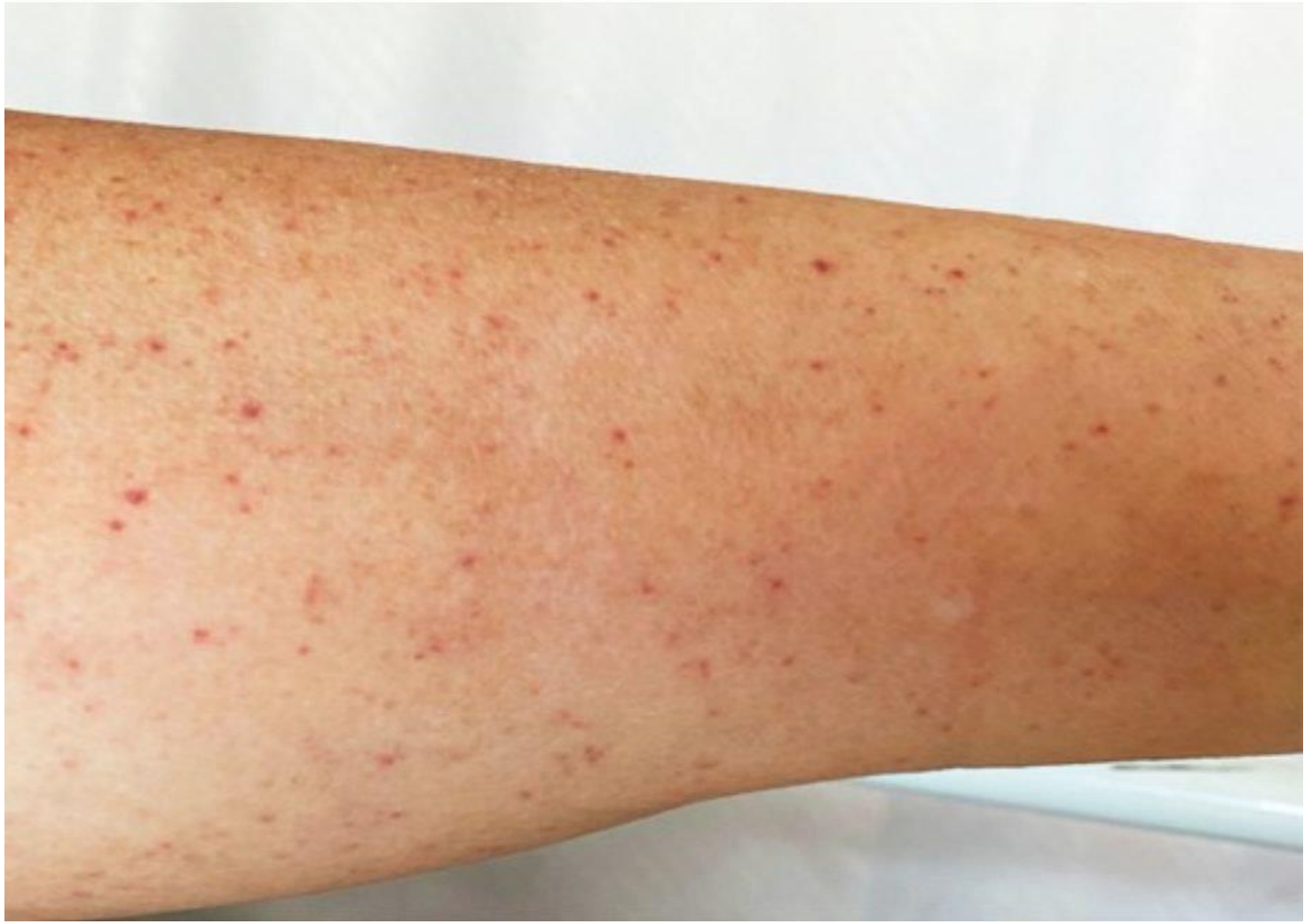


- The normal lifespan of a platelet is **10** days but in ITP this is **reduced** to a few hours.
- Total megakaryocyte mass and platelet turnover are increased in parallel to approximately five times normal.

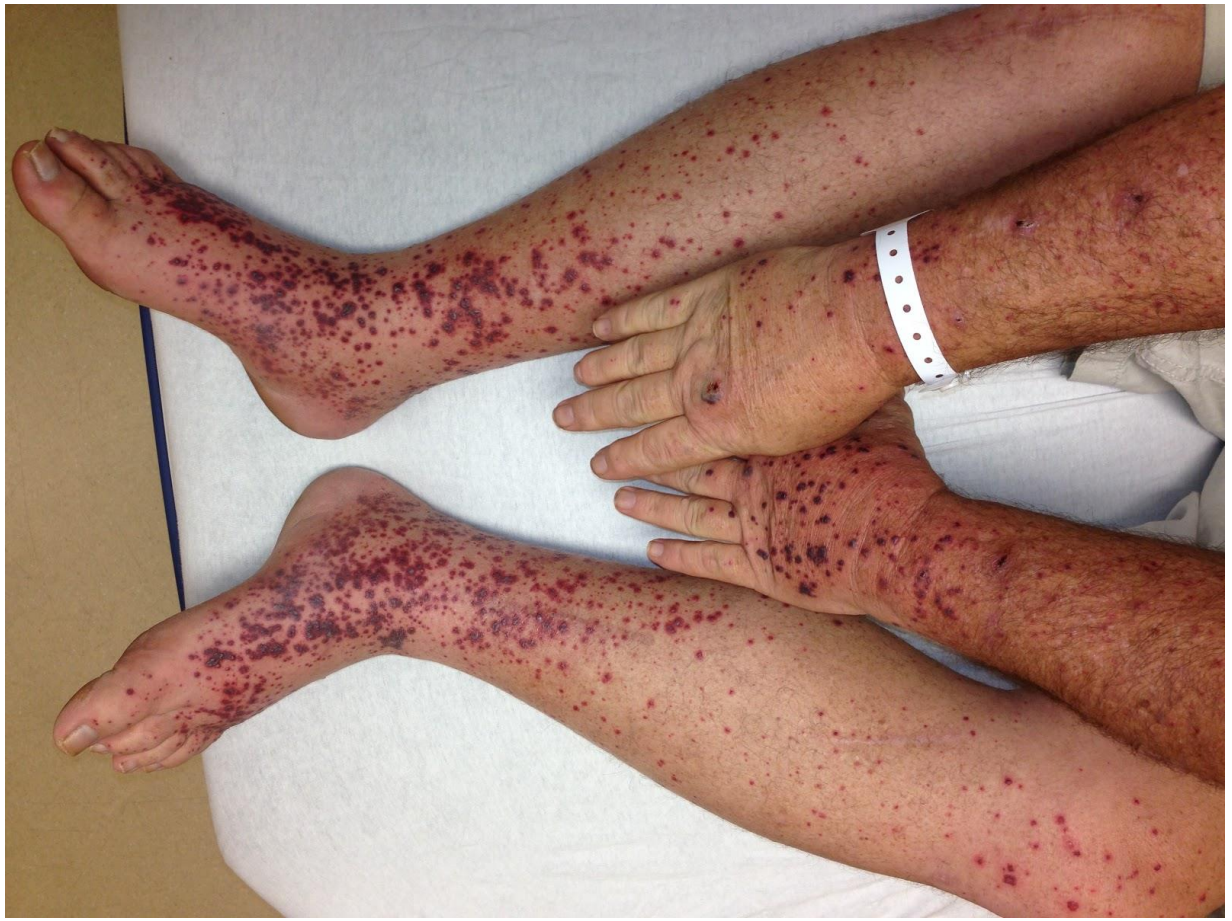
Clinical features:

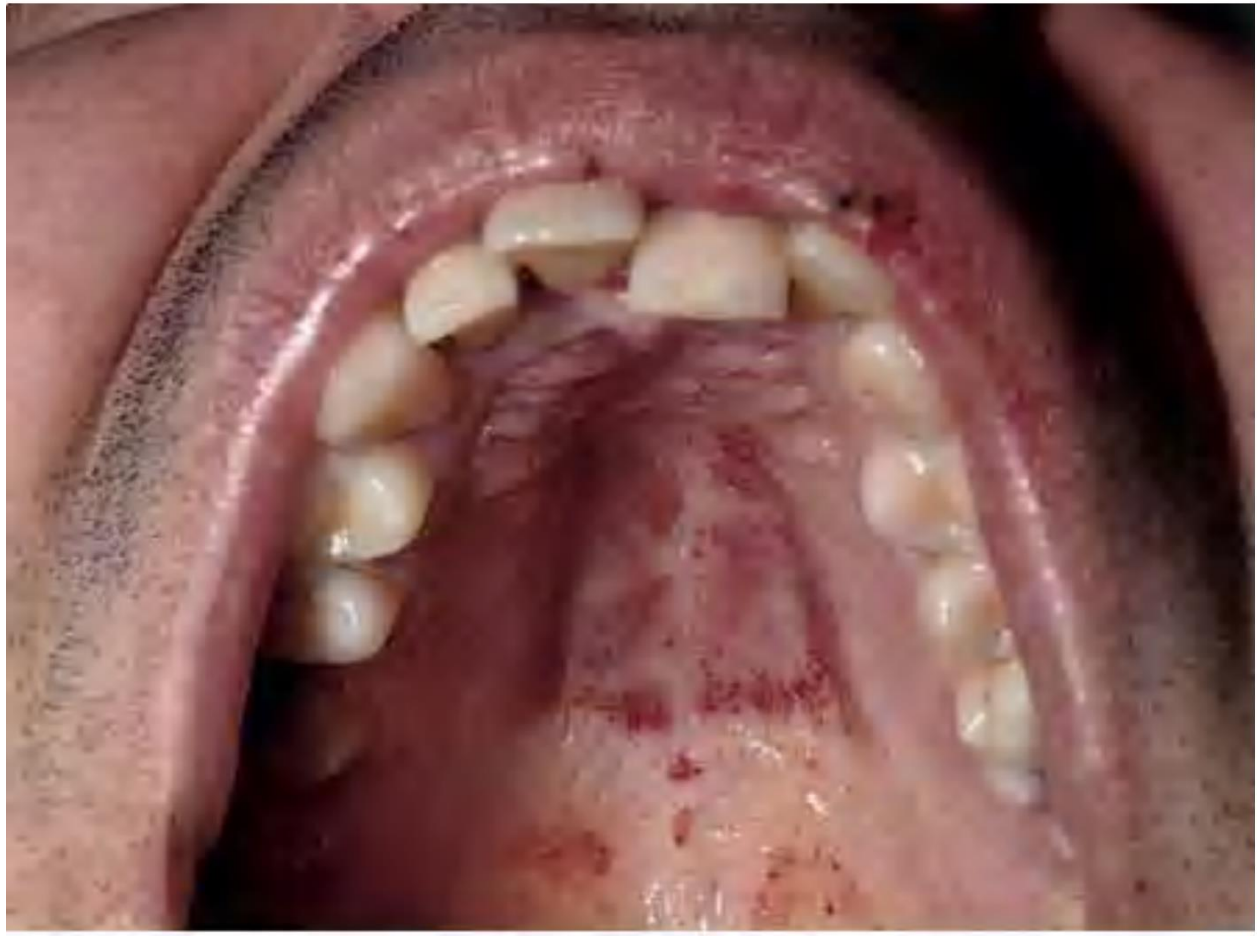
- The onset is often **insidious** with **petechial hemorrhage**, easy bruising and, in women, menorrhagia.
- Mucosal bleeding (e.g. epistaxis or gum bleeding) occurs in severe cases but fortunately intracranial hemorrhage is rare.
- The **severity** of bleeding in ITP is usually **less** than that seen in patients with comparable degrees of thrombocytopenia from bone marrow failure

petechial hemorrhage



Purpura in ITP patient





Thrombocytopenic purpura Can first manifest on the oral mucosa or conjunctiva. Here multiple petechial hemorrhages are seen on the palate.

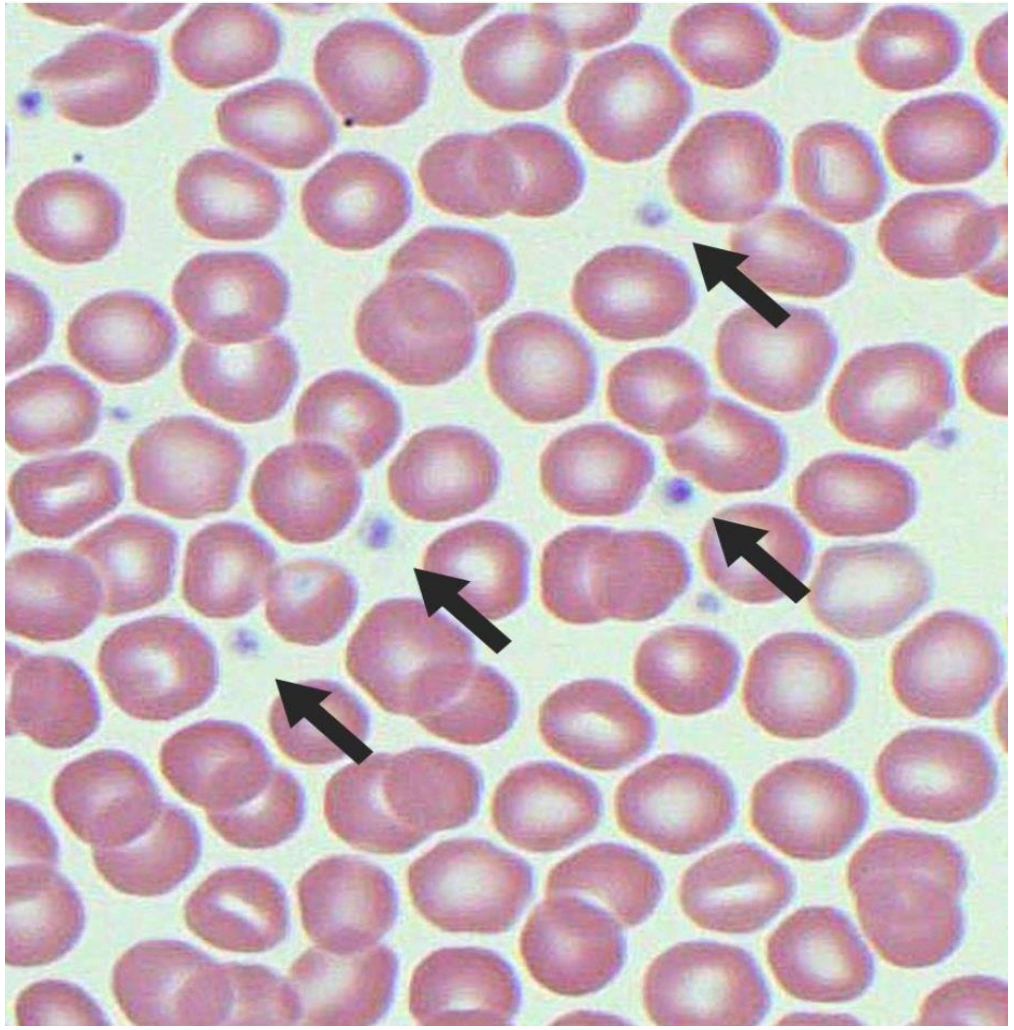
- Chronic ITP tends to **relapse** and **remit** spontaneously so the course may be difficult to predict.
- Many asymptomatic cases are discovered by a routine blood count.
- The spleen is **not palpable** unless there is an associated disease causing splenomegaly.

Diagnosis:

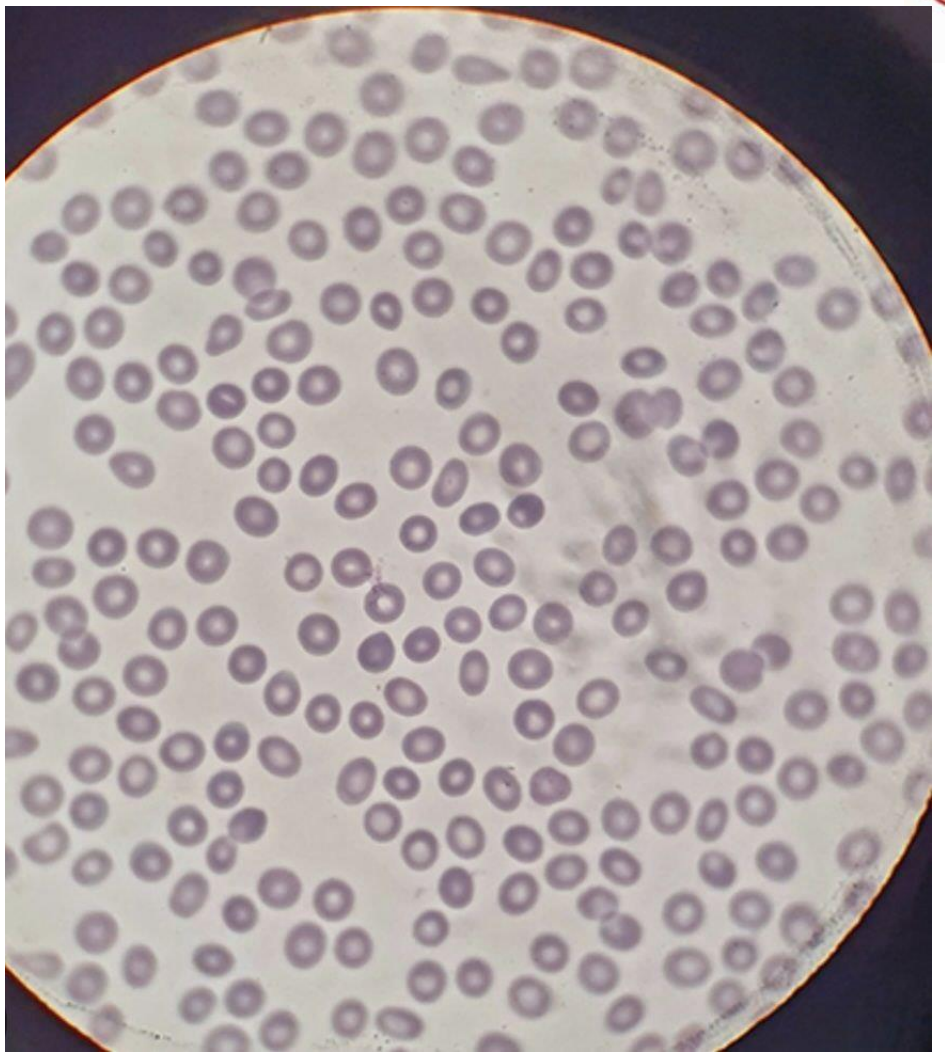
1. **The platelet count** is usually 10–100 × 109/L; The haemoglobin concentration and WBC count are typically normal unless there is iron deficiency anemia because of blood loss.

2. The blood film shows **reduced** numbers of platelets, those present often being large.

Normal blood film



thrombocytopenia



Treatment:

- Corticosteroids
- High-dose intravenous immunoglobulin therapy
- Monoclonal antibody: Rituximab (anti-CD20)
- Immunosuppressive drugs (e.g. vincristine, cyclophosphamide, azathioprine
- Thrombopoietin-receptor agonists.
- Splenectomy ***With the increase in number of alternative drugs, splenectomy is now performed less frequently for ITP than previously***

Acute idiopathic thrombocytopenic purpura

- This is most common in children.
- In approximately 75% of patients the episode follows vaccination or an infection such as chickenpox or infectious mononucleosis.
- Most cases are caused by **non-specific immune complex** attachments to platelets.
- **Spontaneous remissions are usual** but in 5–10% of cases the disease becomes chronic, lasting more than 6 months.

- Q. **Which one of the following laboratory determinations is abnormal in idiopathic thrombocytopenic purpura?**
- a. Partial thromboplastin time (PTT).
- b. platelet count.
- c. Coagulation time.
- d. Prothrombin time (PT).
- e. Thrombin time.

- Q/A 30 year old female, went to her doctor because she had noticed:
- Bruising on her arms and legs for 3-4 days.
- She had NO Fever or other evidence of Infection and did NOT admit to taking any Medications.
- The examination revealed that she was a healthy looking young woman with Bruising and Petechiae on her arms and legs.
- The spleen was NOT palpable.
- Lymph nodes were NOT enlarged.

What is your differential diagnosis?

- Spontaneous bruising could be caused by a:
- **Decreased Platelet Count (Thrombocytopenia).**
- **Abnormal Platelet Function.**
- **Inflammation of Blood Vessels (Vasculitis) resulting in leakage of red cells into the skin.**

What Lab Investigations should be performed?

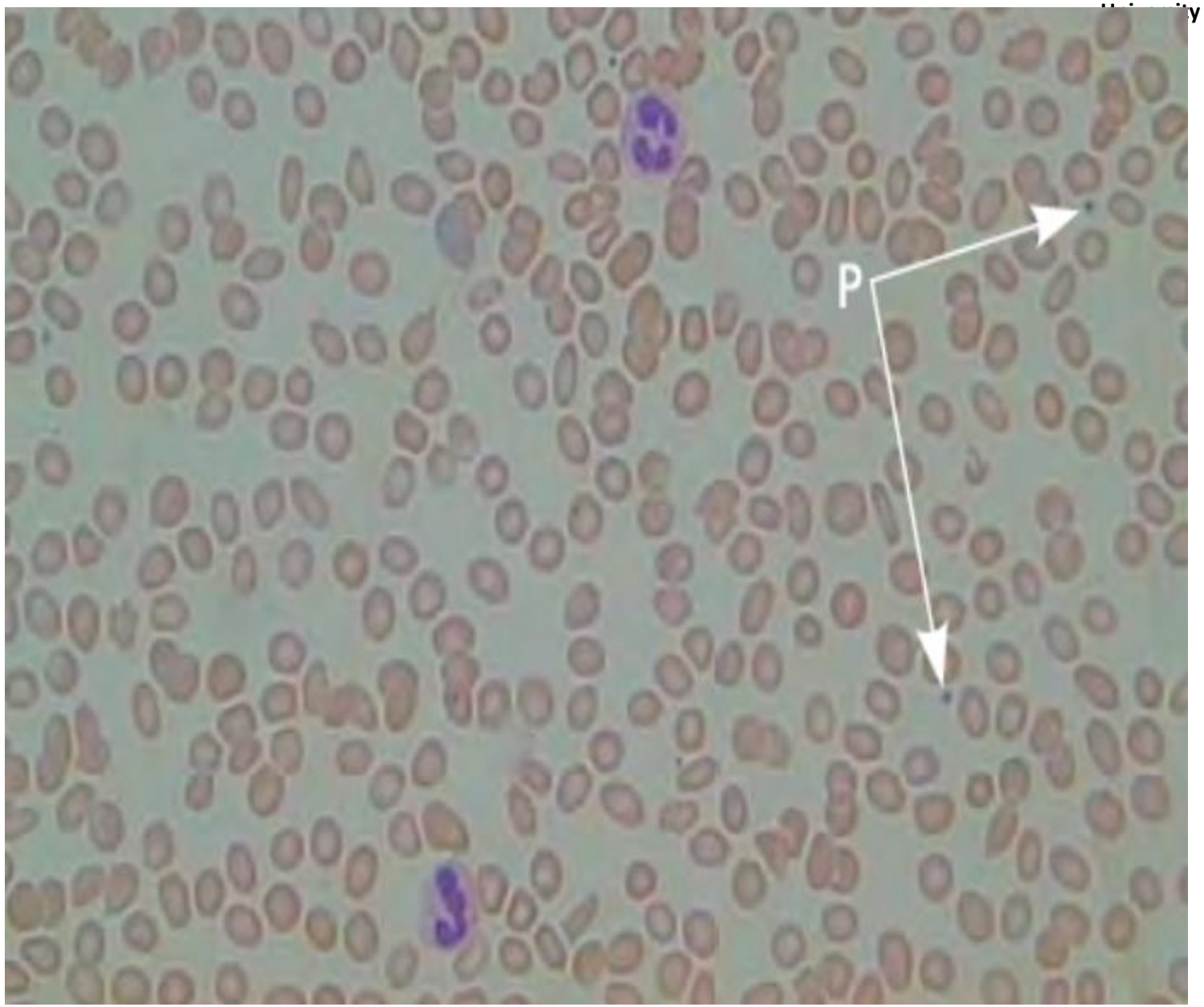
- **Full Blood Count.**
- **Blood Film.**
- **Coagulation Screen**

Her blood count:

	Patient's Results	Normal Range
Hb	12.0 g/dL	11.5-16.5 g/dL
WBC	5×10^9/L	4.0-11.0 $\times 10^9$/L
Platelets	15×10^9/L	150-450 $\times 10^9$/L

Screening tests

	Patient's Results	Normal Range
Prothrombin Time (PT)	12.0 secs	10.0-14.0 secs
Activated Partial Thromboplastin Time (APTT)	33.0 secs	30.0-40.0 secs
Bleeding Time PFA-100	13.0 mins Abnormal	3-8 mins



blood film

Now what is your differential diagnosis?

- **The probability now is that of Immune Platelet Destruction**.

- The absence of physical signs other than purpura.
- The normal hemoglobin and white cell count.
- Make the diagnosis of a hematological malignancy or cancer unlikely.

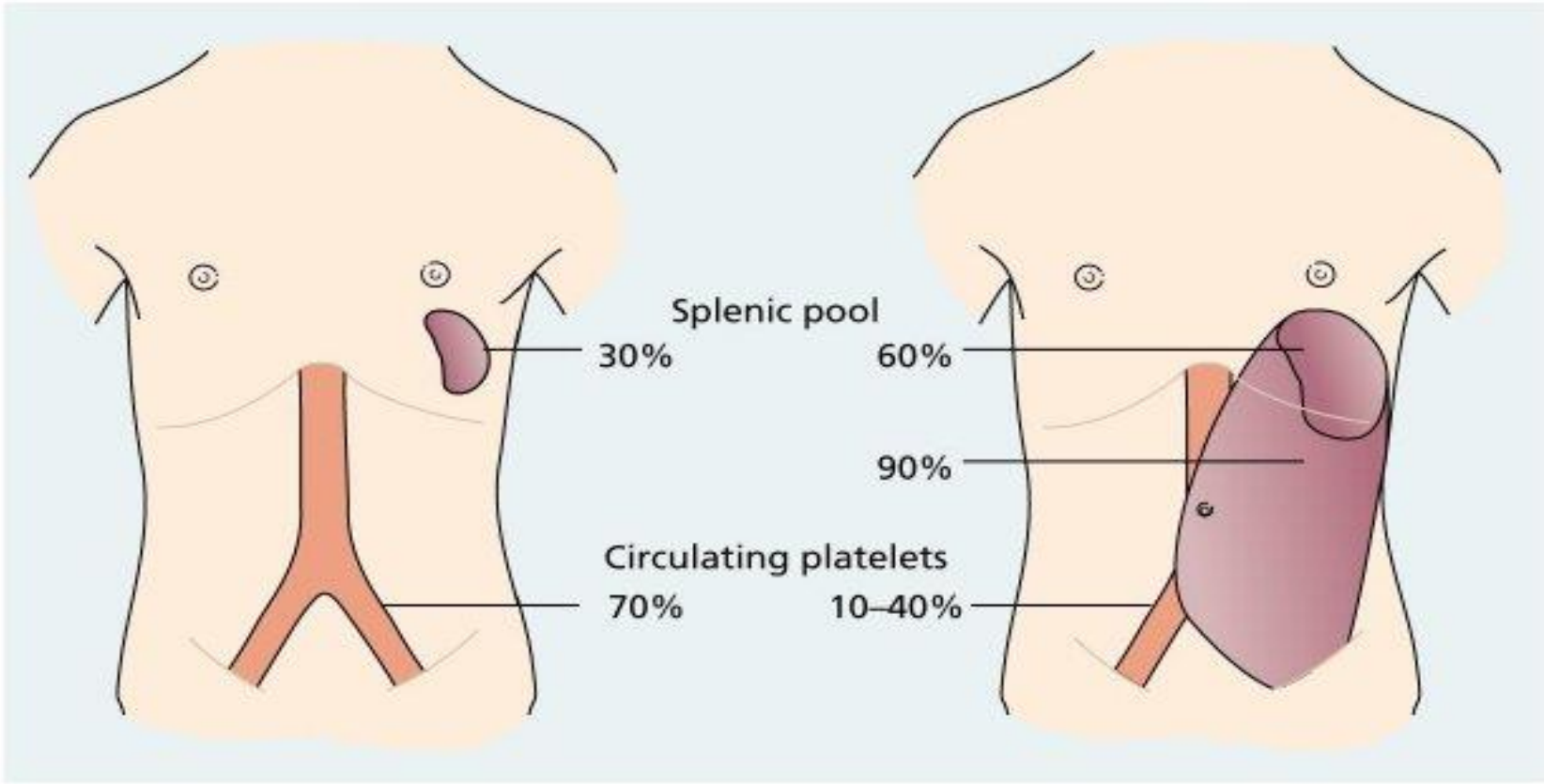
Non immune destruction of platelets

- may be caused by: Mechanical injury in a manner analogous to red cell destruction in microangiopathic hemolytic anemia.

- The underlying conditions are also similar, including prosthetic heart valves and diffuse narrowing of the micro vessels (e.g., malignant hypertension).

Increased splenic pooling

- The major factor responsible for thrombocytopenia in splenomegaly is platelet ‘pooling’ by the spleen.
- In splenomegaly, up to 90% of platelets may be sequestered in the spleen, whereas normally this accounts for approximately one-third of the total platelet mass.


Splenic pool
30%
60%
90%
Circulating platelets
70%
10–40%

- Platelet lifespan is normal and, in the absence of additional hemostatic defects, the thrombocytopenia of splenomegaly is not usually associated with bleeding.

Dilutional thrombocytopenia :

Massive transfusions can produce a dilutional thrombocytopenia.

Blood stored for longer than 24 hours contains virtually no viable platelets; thus, plasma volume and red cell mass are reconstituted by transfusion, but the number of circulating platelets is relatively reduced.

Drug induced thrombocytopenia

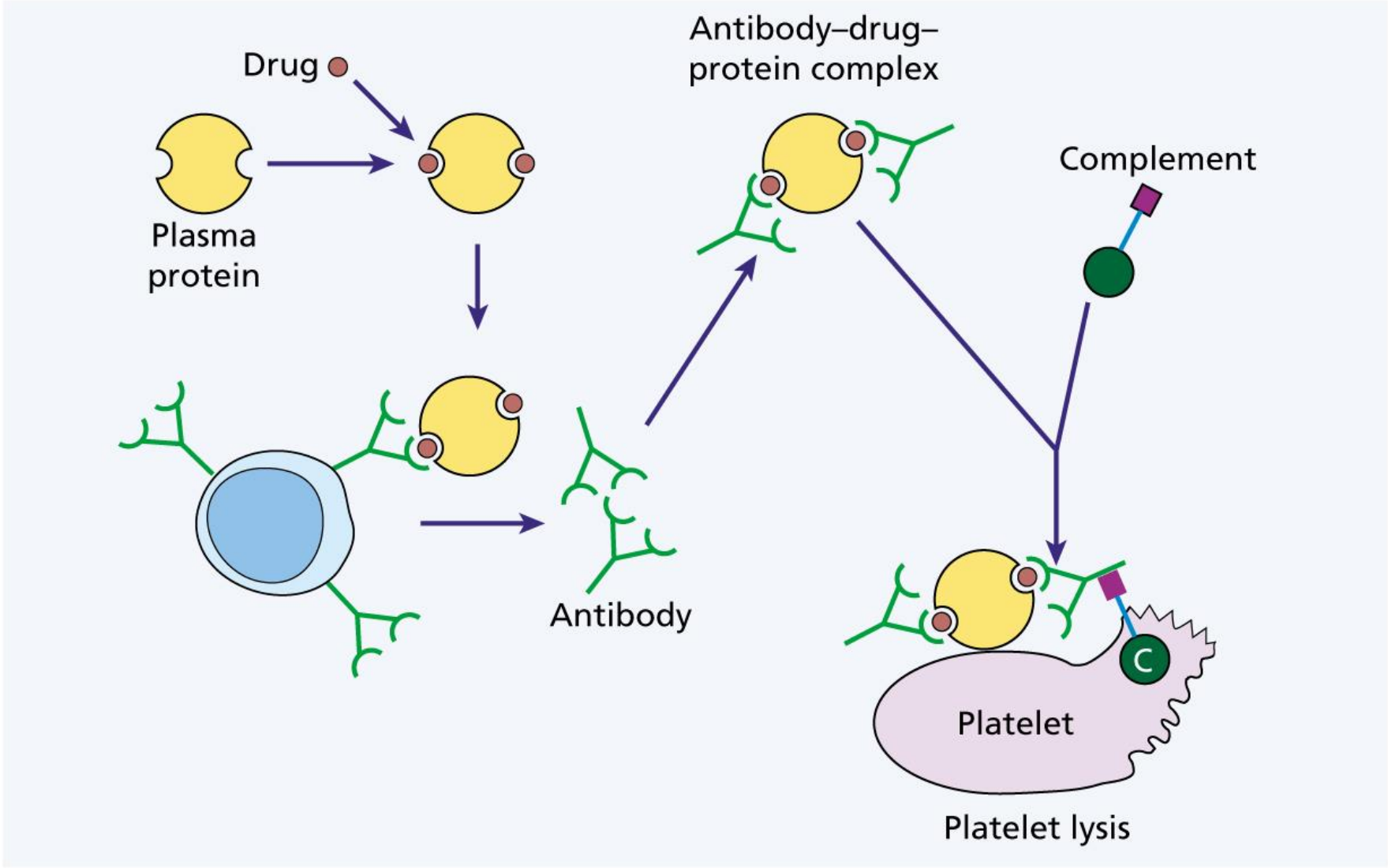
An antibody-drug-protein complex is deposited on the platelet surface.

If **complement** is attached and the sequence goes to completion, the platelet may be lysed **directly.**

Otherwise, it is removed by reticuloendothelial cells because of opsonization with immunoglobulin and / or the C3 component of complement.

Quinine, quinidine and heparin are particularly common causes.

Mechanism of drug induced thrombocytopenia



Defects in platelets function

Qualitative defects of platelet function can be:

1-congenital or

2-acquired

Congenital disorders of platelet function can be classified into three groups on the basis of the specific functional abnormality:

1. Defects of adhesion.

2. Defects of aggregation.

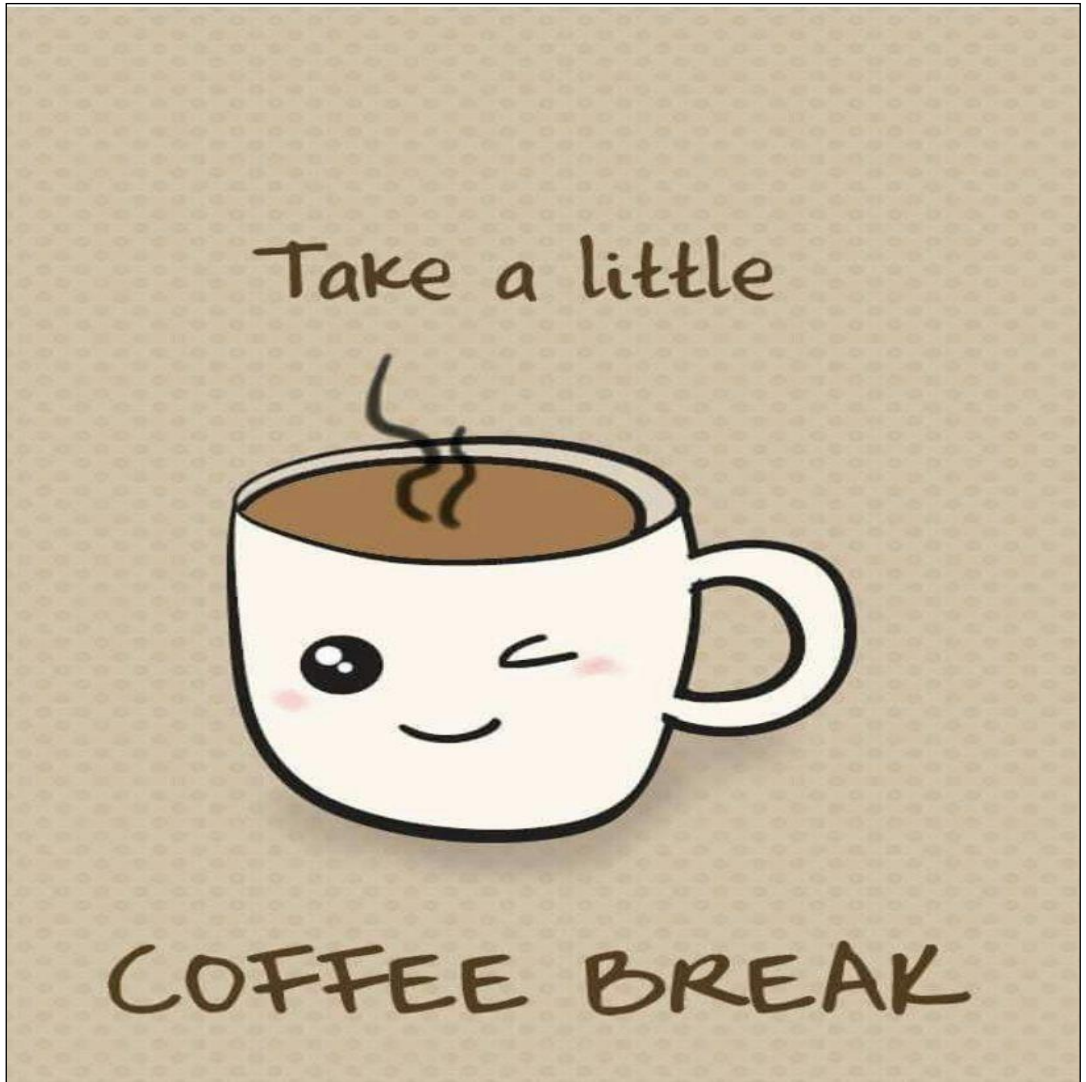
3. Disorders of platelet secretion (release reaction).

Several congenital disorders characterized by

Prolonged bleeding time

Abnormal PFA-test

Normal platelet count.


Take a little
COFFEE BREAK


tea time

Acquired disorders

- Aspirin therapy is the **most common** cause of defective platelet function.
- It produces **abnormal** closure times in the platelet function analysis-100 **(PFA-100) test** and, although purpura may not be obvious, the defect may contribute to the associated gastrointestinal hemorrhage.

- **Dipyridamole** inhibits platelet aggregation by blocking reuptake of adenosine and is usually used as an adjunct to aspirin.
- **Clopidogrel** and **prasugrel** inhibit binding of ADP to its platelet receptor shown by impaired aggregation with ADP

Hyperglobulinemia:

- Hyperglobulinemia associated with multiple myeloma or Waldenström's disease may cause interference with platelet adherence, release and aggregation.

Myeloproliferative and myelodysplastic disorders:

- Intrinsic abnormalities of platelet function occur in many patients with essential thrombocythemia, other myeloproliferative and myelodysplastic diseases and in paroxysmal nocturnal hemoglobinuria.

Uraemia: This is associated with various abnormalities of platelet function

Platelet transfusions

- ***Transfusion of platelet concentrates is indicated in the following circumstances***:
- Thrombocytopenia or abnormal platelet function when bleeding or before invasive procedures and where there is no alternative therapy available.
- The platelet count should be above 50 × 109/L before, for example, liver biopsy or lumbar puncture.
- Prophylactically in patients with platelet counts of less than 5–10 × 109/L. If there is infection, potential bleeding sites or coagulopathy, the count should be kept above 20 × 109/L.

Hereditary coagulation disorders

- Hereditary deficiencies of each of the coagulation factors have been described.

- Haemophilia A (factor VIII deficiency), haemophilia B (Christmas disease, factor IX deficiency) and von Wille brand disease (VWD) are the most frequent; the others are rare.

Haemophilia A

- Haemophilia A is the **most common** of the hereditary clotting factor deficiencies.
- The inheritance is **sex-linked**, but up to one-third of patients have no family history and these cases result from recent mutation.

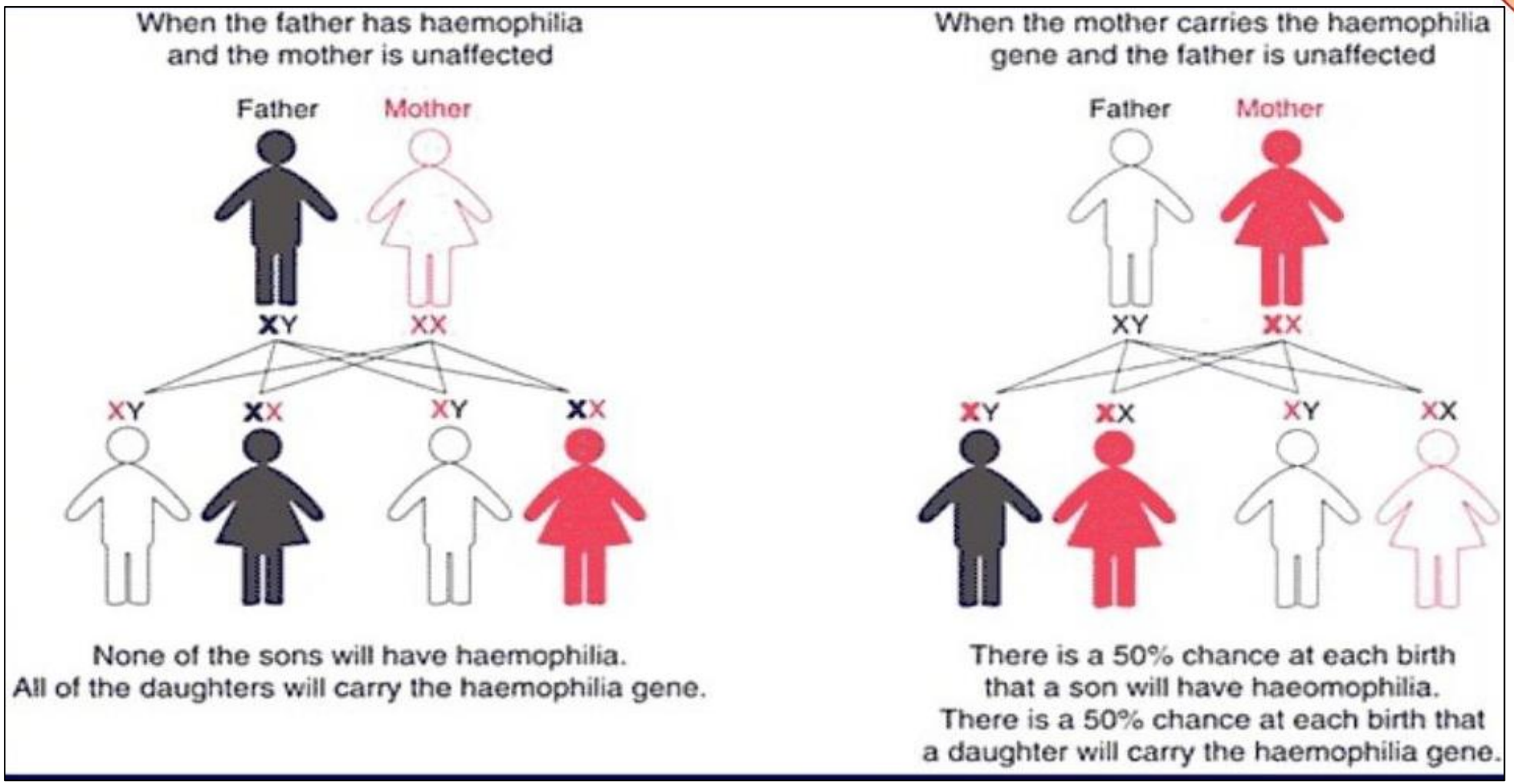
Can the female manifest the disease?

Molecular genetics

- The defect is an absence or low level of plasma factor VIII. Approximately half of the patients have missense or frameshift mutations or deletions in the factor VIII gene.

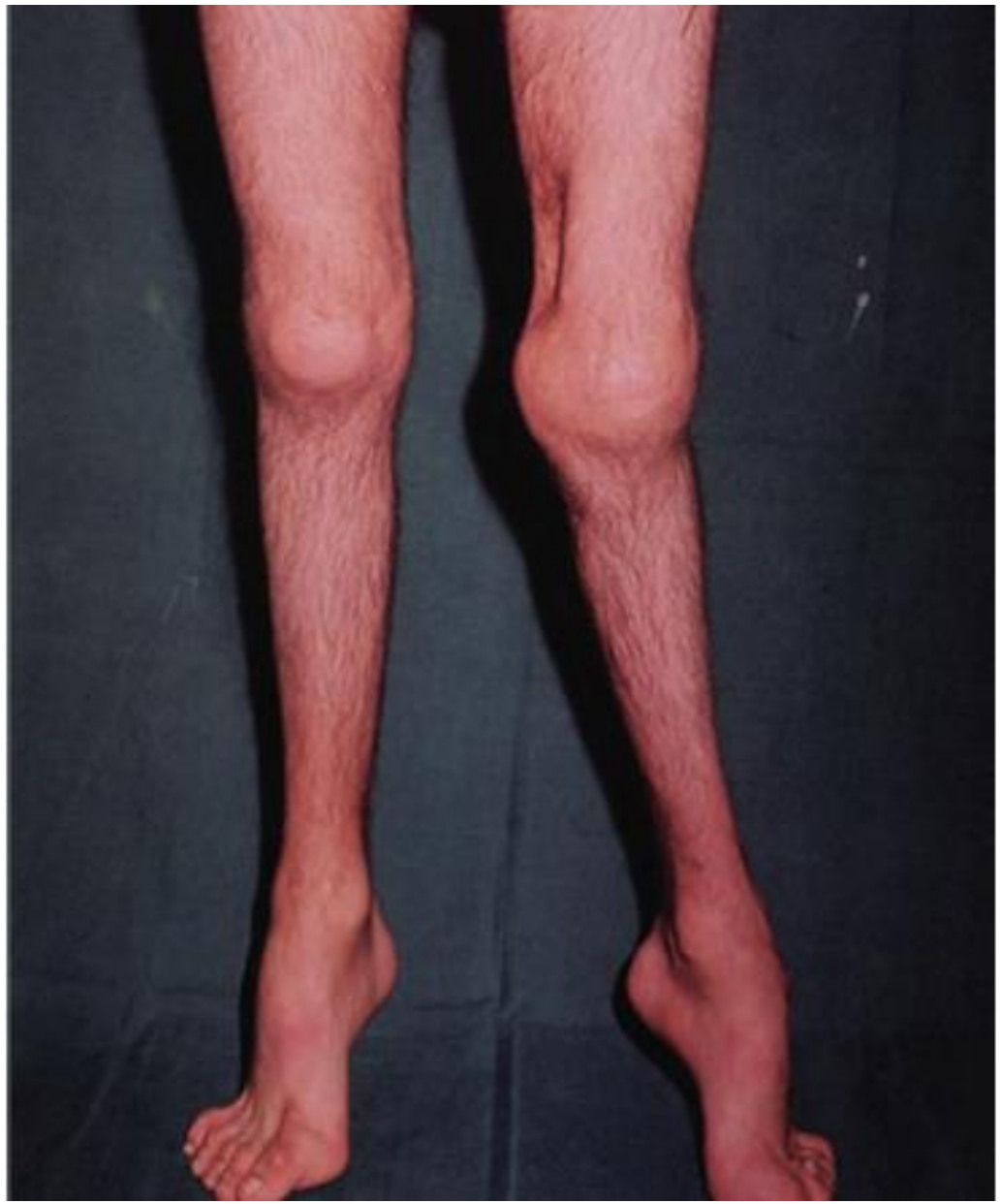
- If the mother is a carrier of hemophilia gene and the father is unaffected, what are the possibilities for the offspring?

Genetics of hemophilia



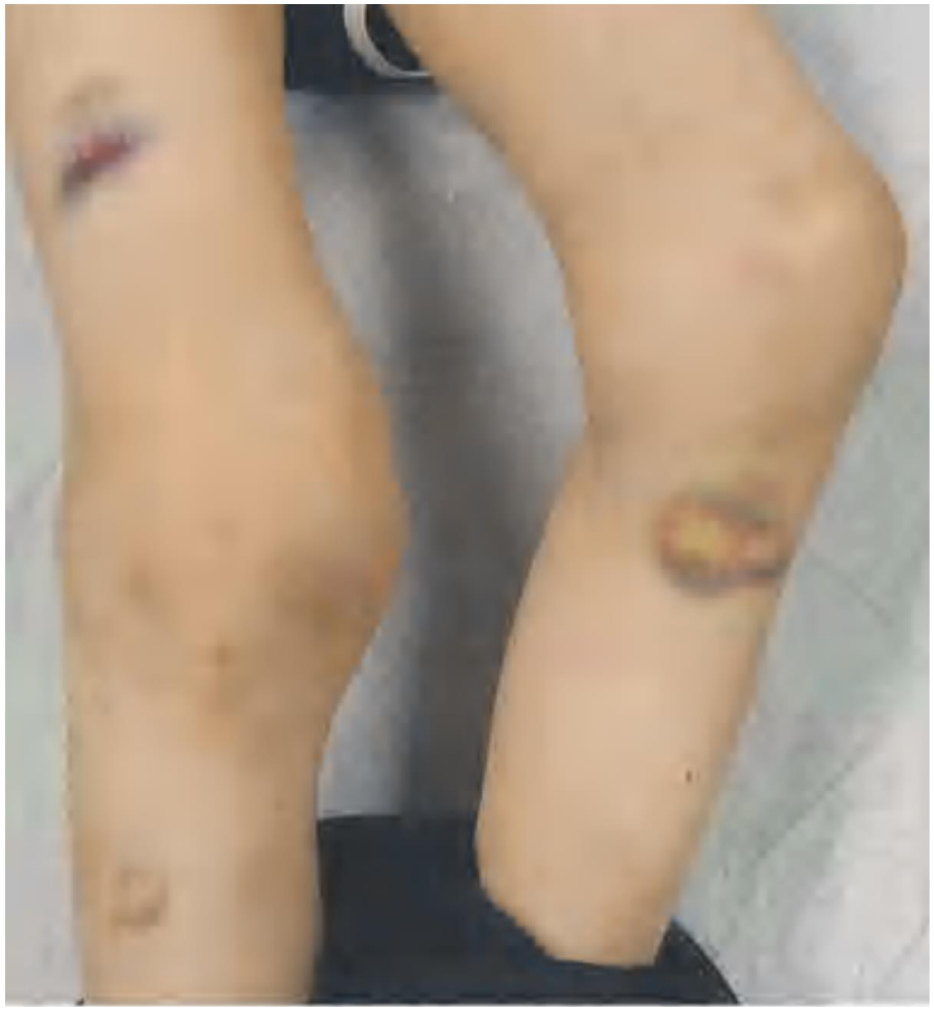
Clinical features:

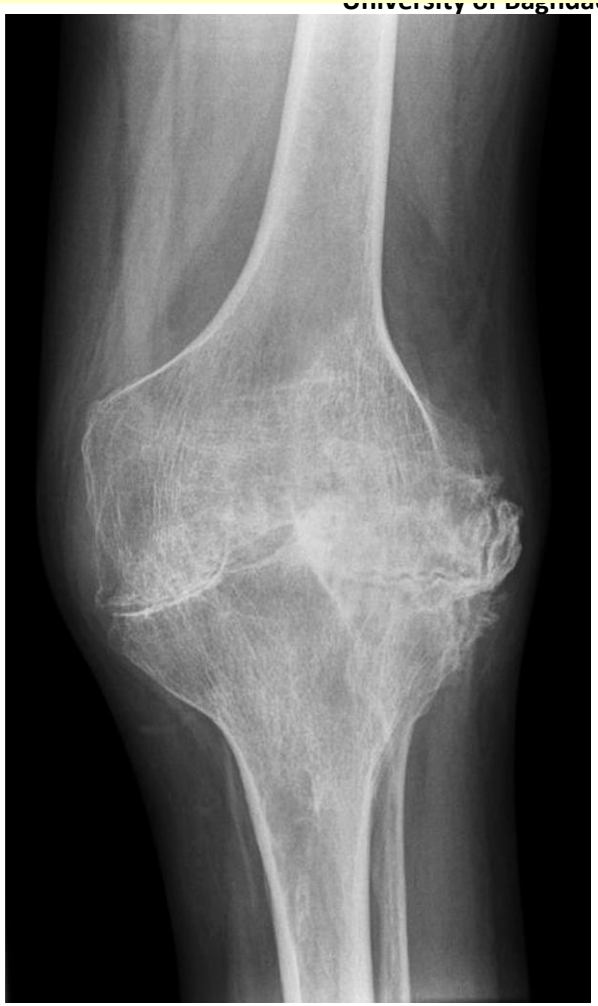
- Infants may develop profuse post-circumcision haemorrhage or joint and soft tissue bleeds and excessive bruising when they start to be active.
- Recurrent painful haemarthroses and muscle haematomas dominate the clinical course of severely affected patients and, if inadequately treated, lead to progressive joint deformity and disability.



Haemophilia A showing severe disability. The left knee is swollen with posterior subluxation of the tibia on the femur.

Hemophilia A: Hemarthrosis





Chronic right knee hemarthrosis with fresh and fading ecchymoses on legs. Radiological image of knee showing loss of joint space with apparent fusion of femoral and tibial articulation and cystic changes.

- Prolonged bleeding occurs after dental extractions.
- Spontaneous haematuria and gastrointestinal haemorrhage, sometimes with obstruction resulting from intramucosal bleeding, can also occur.
- The clinical severity of the disease correlates inversely with the factor VIII level

- Hemophilia A exhibits a wide range of clinical severity that correlates well with the level of factor VIII activity.

- Those with less than 1% of normal activity develop severe disease.
- Levels between 2% and 5% of normal are associated with moderate disease.
- Patients with 6% to 50% of activity develop mild disease

Table 26.1 Correlation of coagulation factor activity and disease severity in haemophilia A or B.

Coagulation factor activity (percentage of normal)	Clinical manifestations
<1	Severe disease Frequent spontaneous bleeding into joints, muscles, internal organs from early life Joint deformity and crippling if not adequately prevented or treated
1–5	Moderate disease Bleeding after minor trauma Occasional spontaneous episodes
>5	Mild disease Bleeding only after significant trauma, surgery

Laboratory findings:

- The following tests are **abnormal**:
- 1 Activated partial thromboplastin time (**APTT**).
- 2 Factor **VIII clotting assay**.

- The platelet function analysis-100 (PFA-100) and prothrombin time (PT) are normal

Q/ A 25-year-old man has a lifelong hemorrhagic diathesis. The Prothrombin time (PT), bleeding time and PFA-100 test are normal, but the Partial thromboplastin time (PTT) is prolonged. The most likely cause of the bleeding disorder is:

a. Factor VIII deficiency.
b. Factor X deficiency.
c. Factor VII deficiency.
d. A platelet functional disorder.
e. von Willbrand disease.

Q/A 13-year-old male has less than 1% factor VIII activity measured in plasma. If he does not receive transfusions of factor VIII concentrate, which of the following manifestations of this deficiency is most likely to ensue?

a. Splenomegaly.
b. Conjunctival petechiae.
c. Hemolysis.
d. Hemochromatosis.
e. Hemarthroses.

Treatment:

- Most patients in developed countries attend specialized haemophilia centers where there is a multidisciplinary team dedicated to their care.
- Bleeding episodes are treated with factor VIII replacement therapy, and spontaneous bleeding is usually controlled if the patient's factor VIII level is raised to 30–50% of normal.

- For major surgery, serious post-traumatic bleeding or when haemorrhage is occurring at a dangerous site, the factor VIII level should be elevated to 100% and then maintained above 50% when acute bleeding has stopped.
- On average, factor VIII infusion produces a plasma increment of 20 U/L for each unit infused/kg body weight.

- Recombinant factor VIII and plasma-derived purified factor VIII preparations, which are heat and solvent-detergent treated, are available for clinical use and have never transmitted viral infections.
- vasopressin (DDAVP) provides an alternative means of increasing the plasma factor VIII level in milder haemophiliacs.

Factor IX deficiency (haemophilia B, Christmas disease)

- The inheritance and clinical features of factor IX deficiency (Christmas disease, haemophilia B) are identical to those of haemophilia A.
- Indeed, the two disorders can only be distinguished by specific coagulation factor assays.
- The principles of replacement therapy are similar to those of haemophilia A.

VWF Disease

Von Willebrand factor (VWF)

- VWF is involved in shear-dependent platelet adhesion to the vessel wall and to other platelets (aggregation) .
- It also carries factor VIII. It is a large glycoprotein, with multimers made up on average of 2–50 dimeric subunits. VWF is synthesized both in endothelial cells and megakaryocytes, and stored in Weibel–Palade bodies and platelet α granules, respectively.
- Plasma VWF is almost entirely derived from endothelial cells.

Von Willebrand disease

- VWD is the most common inherited bleeding disorder.
- Usually, the inheritance is autosomal dominant.
- In this disorder there is either a **reduced level** or **abnormal function** of VWF resulting from a point mutation or major deletion.
- Patients with von Willebrand disease have defects in platelet function despite a normal platelet count.

Laboratory findings

- The PFA-100 test is abnormal.
- Factor VIII levels are often low. If low, a factor VIII/VWF binding assay is performed.
- The APTT may be prolonged.
- VWF levels are usually low.

- Q/A young adult patient has just been diagnosed with Von Willebrand disease.

Which of the following statements should you make to advise the patient of potential consequences of this disease?

- a. You may need an allogeneic bone marrow transplant.
- b. Expect increasing difficulties with joint mobility.
- c. Anticoagulation is needed to prevent deep venous thrombosis.
- d. You may have excessive bleeding following tooth extraction.
- e. A splenectomy may be necessary to control the disease.

Q/All of the following conditions are associated with a prolonged bleeding time EXCEPT:

a. von Will brand disease.

b. Deficiency of factor IX.

c. Long-term treatment with aspirin.

d. Idiopathic thrombocytopenic purpura.

e. Defect in platelet adhesion.

Acquired coagulation disorders

The acquired coagulation disorders are more common than the inherited disorders.

Vitamin K deficiency:

Fat-soluble vitamin K is obtained from green vegetables and bacterial synthesis in the gut. Deficiency may present in the newborn (haemorrhagic disease of the newborn) or in later life

Table 26.4 The acquired coagulation disorders.

Deficiency of vitamin K-dependent factors

- Haemorrhagic disease of the newborn
- Biliary obstruction
- Malabsorption of vitamin K (e.g. tropical sprue, gluten-induced enteropathy)
- Vitamin K-antagonist therapy (e.g. coumarins, indandiones)
- Liver disease – complex dysregulation with synthetic failure of pro- and anticoagulant factors
- Disseminated intravascular coagulation – consumption of all clotting factors and platelets

Inhibition of coagulation

- Specific inhibitors (e.g. antibodies against factor VIII)
- Non-specific inhibitors (e.g. antibodies found in systemic lupus erythematosus, rheumatoid arthritis which paradoxically cause thrombosis)

Miscellaneous

- Diseases with M-protein production that interfere with haemostasis
- L-Asparaginase
- Therapy with heparin, defibrinating agents or thrombolytics
- Massive transfusion syndrome

Vitamin K deficiency:

- Deficiency of vitamin K is caused by:
- an inadequate diet.
- malabsorption .
- inhibition of vitamin K by vitamin K antagonist drugs such as warfarin.
- Warfarin is associated with a decrease in the functional activity of factors II, VII, IX and X and proteins C and S, but immunological methods show normal levels of these factors.

Haemorrhagic disease of the newborn

- Vitamin K-dependent factors are **low at birth** and fall further in **breast-fed infants** in the first few days of life.
- Liver cell immaturity, lack of gut bacterial synthesis of the vitamin and low quantities in breast milk may all contribute to a deficiency which causes haemorrhage, usually on the second to fourth day of life
- but occasionally during the first 2 months.

Diagnosis

- The PT and APTT are both abnormal.
- The platelet count and fibrinogen are normal with absent fibrin degradation products.

Treatment

- Prophylaxis. For many years vitamin K has been given to all newborn babies as a **single intramuscular injection of 1 mg**. This remains the most appropriate and safest treatment.

- In bleeding infants: vitamin K 1 mg intramuscularly is given every 6 hours with, initially, prothrombin complex concentrate if haemorrhage is severe.

Disseminated intravascular coagulation

- Widespread inappropriate intravascular deposition of fibrin with consumption of coagulation factors and platelets occurs as a consequence of many disorders that release procoagulant material into the circulation or cause wide spread endothelial damage or platelet aggregation.

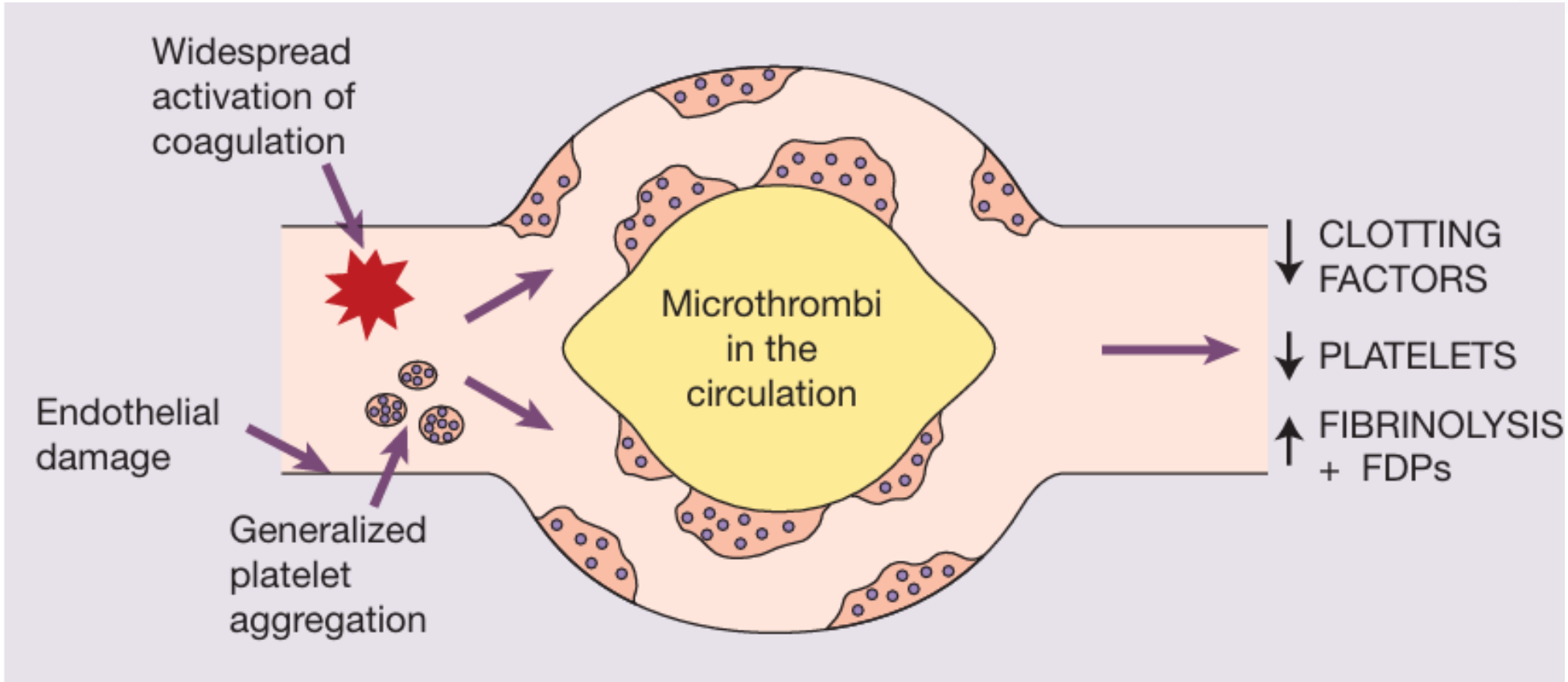
- It may be associated with a fulminant haemorrhagic or thrombotic syndrome with organ dysfunction or run a less severe and more chronic course.
- The **main** clinical presentation is with **bleeding** but 5–10% of patients manifest thrombotic lesions

pathogenesis

- The key event underlying DIC is increased activity of thrombin in the circulation that overwhelms its normal rate of removal by natural anticoagulants.
- This can come from **tissue factor (TF) release into the circulation** from damaged tissues present on tumor cells or from up-regulation of TF on circulating monocytes or endothelial cells in response to pro inflammatory cytokines (e.g. IL-1, TNF, endotoxin).

- DIC may be triggered by the entry of procoagulant material into the circulation in the following situations:
- severe trauma.
- amniotic fluid embolism.
- premature separation of the placenta.
- widespread mucin-secreting adenocarcinomas.
- acute promyelocytic leukemia.
- Sepsis.

- DIC may also be initiated by widespread endothelial damage and collagen exposure (e.g. endotoxaemia, Gram-negative and meningococcal septicaemia, septic abortion), certain virus infections and severe burns or hypothermia.


Widespread activation of coagulation
Endothelial damage
Generalized platelet aggregation
Microthrombi in the circulation
CLOTTING FACTORS
PLATELETS
FIBRINOLYSIS + FDPs

Clinical features

- These are usually dominated by bleeding, particularly from venepuncture sites or wounds.
- There may be generalized bleeding in the gastrointestinal tract, the oropharynx, into the lungs, urogenital tract and in obstetric cases, vaginal bleeding may be particularly severe.
- Less frequently, micro thrombi may cause skin lesions, renal failure, gangrene of the fingers or toes or cerebral ischemia.

Laboratory findings

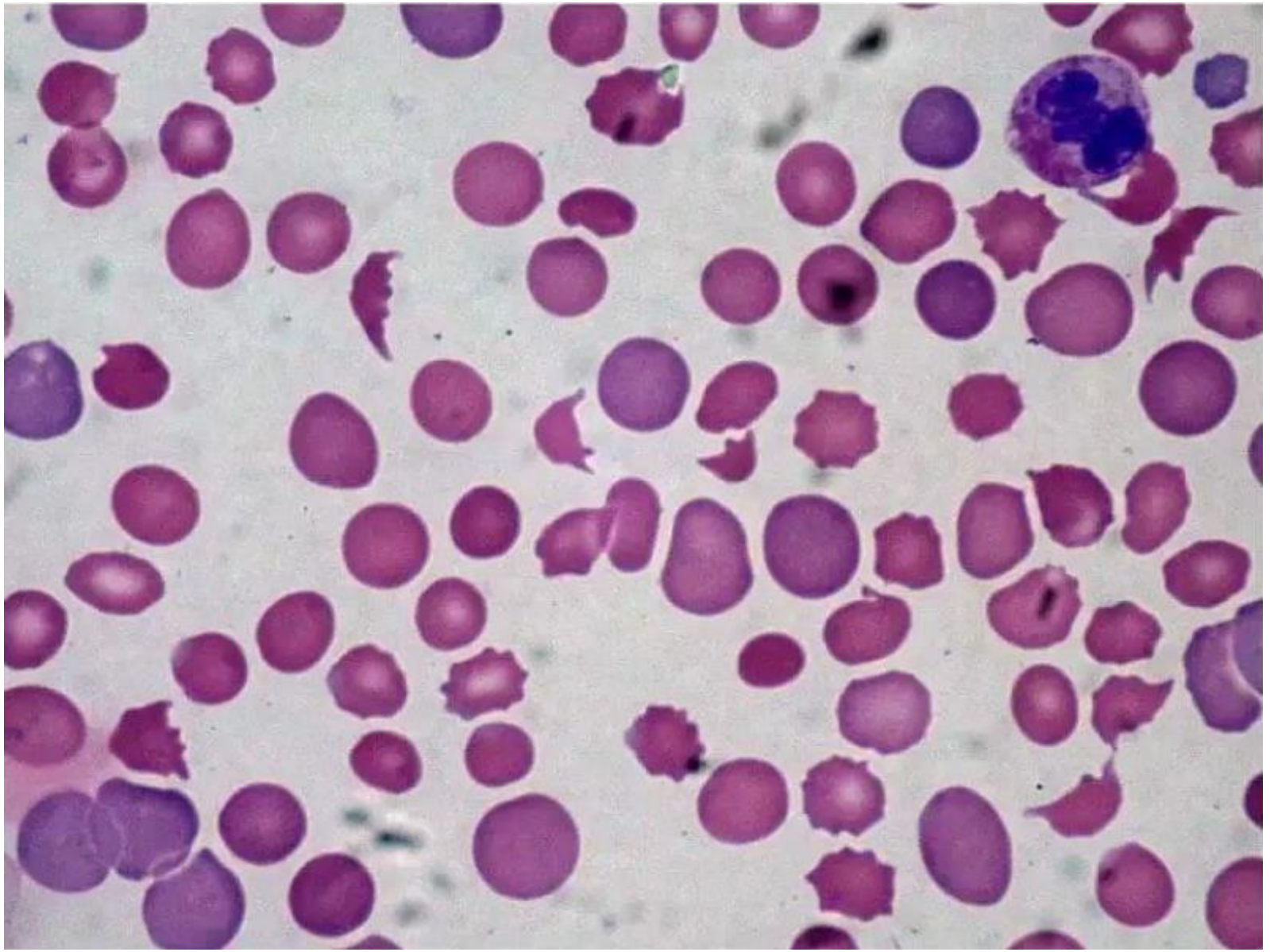
- In many acute syndromes the blood may fail to clot because of gross fibrinogen deficiency.

Tests of haemostasis

- 1 The platelet count is low.
- 2 Fibrinogen concentration is low.
- 3 The thrombin time is prolonged.
- 4 High levels of fibrin degradation products such as D-dimers are found in serum and urine.
- 5 The PT and APTT are prolonged in the acute syndromes.

Blood film examination

- In many patients there is a haemolytic anaemia (‘microangiopathic’) and the red cells show prominent fragmentation.



- red cells show prominent fragmentation

Treatment

- Treatment of the underlying cause is **most important**.
- The management of patients who are bleeding differs from that of patients with thrombotic problems.

Bleeding:

- Supportive therapy with fresh frozen plasma and platelet concentrates is indicated in patients with dangerous or extensive bleeding.
- Cryoprecipitate or fibrinogen concentrates provide more concentrated fibrinogen.
- red cell transfusions may be required.

Thrombosis :

- The use of heparin or antiplatelet drugs to inhibit the coagulation process is considered in those with thrombotic problems such as skin ischemia.
- Fibrinolytic inhibitors should not be used. Why?


Thank you