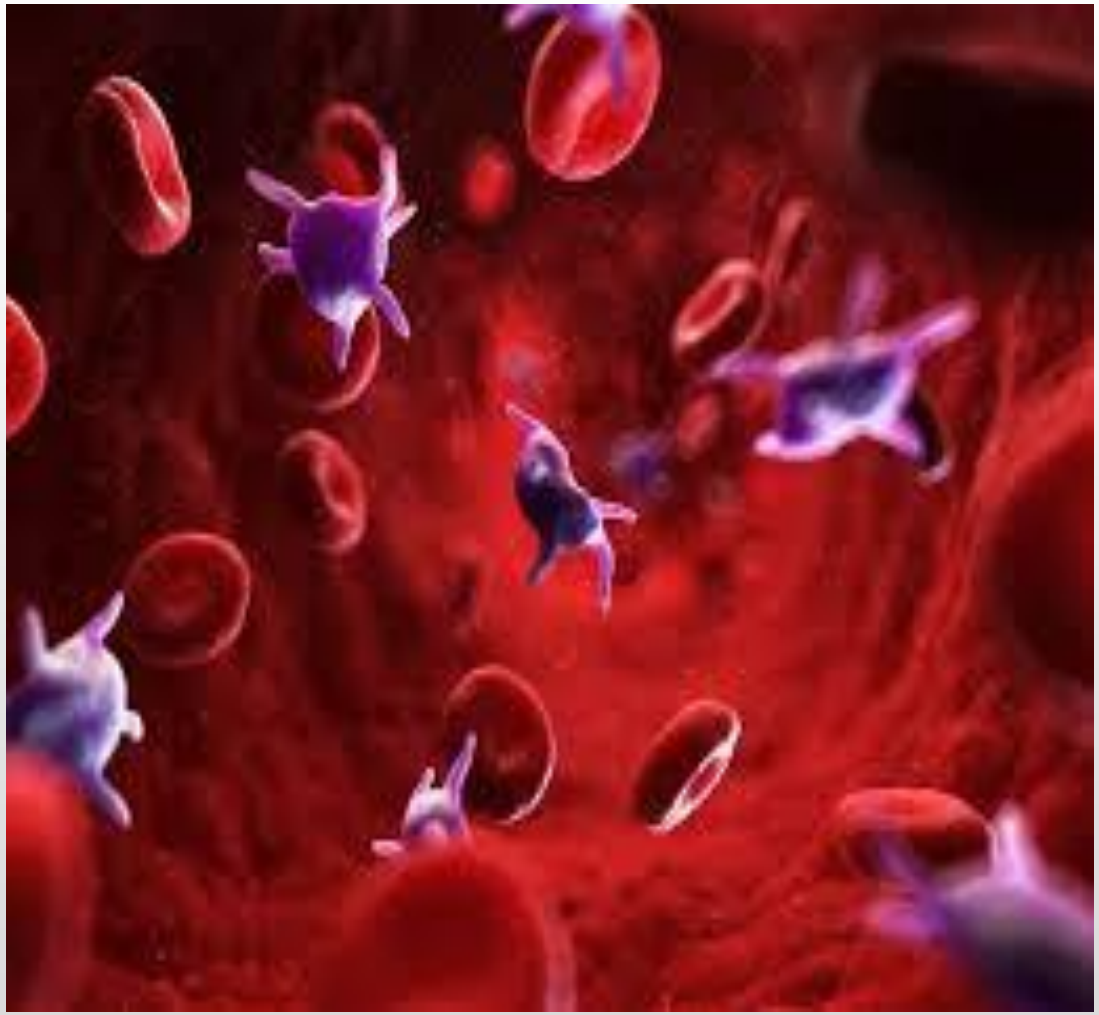
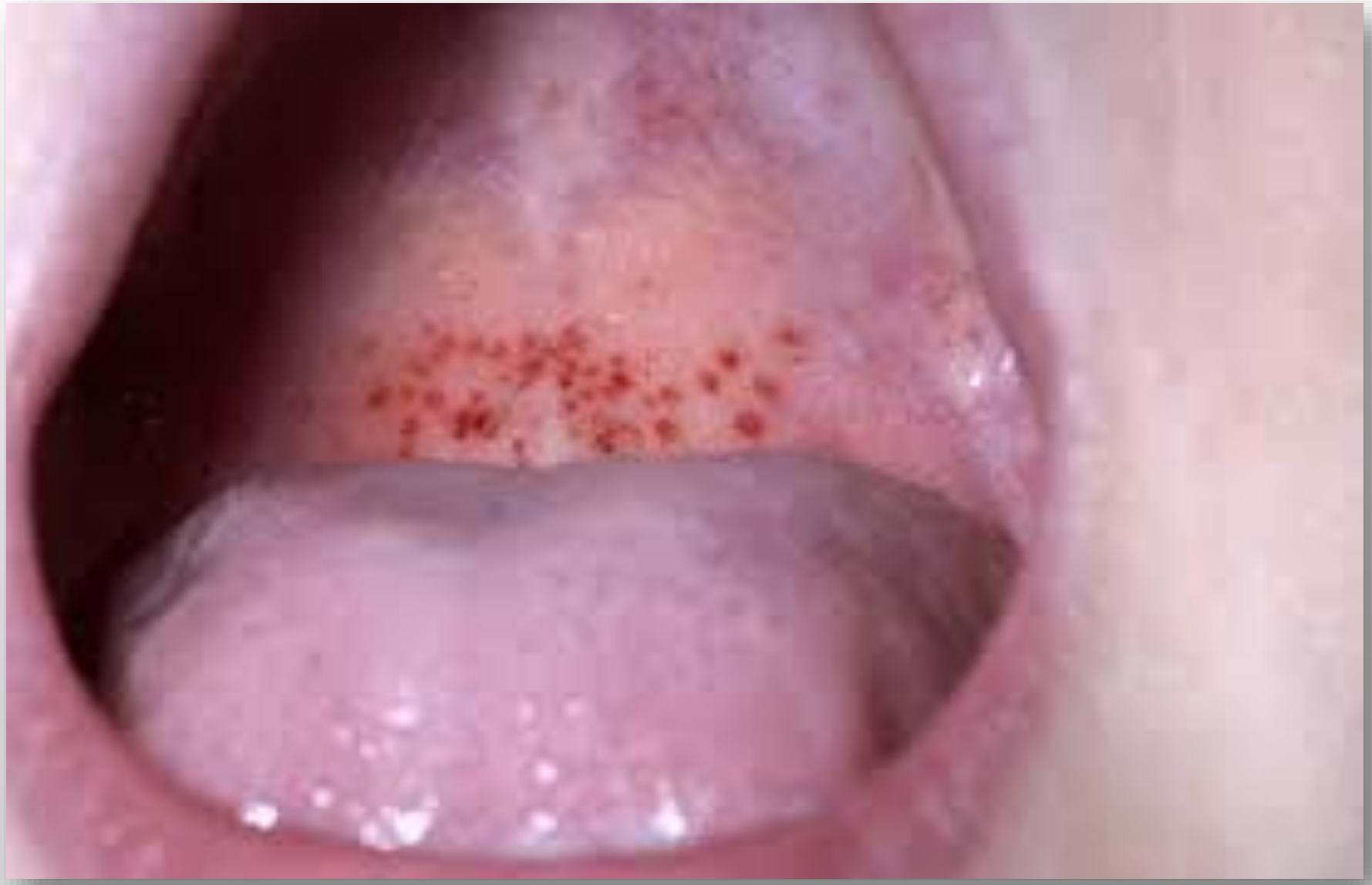


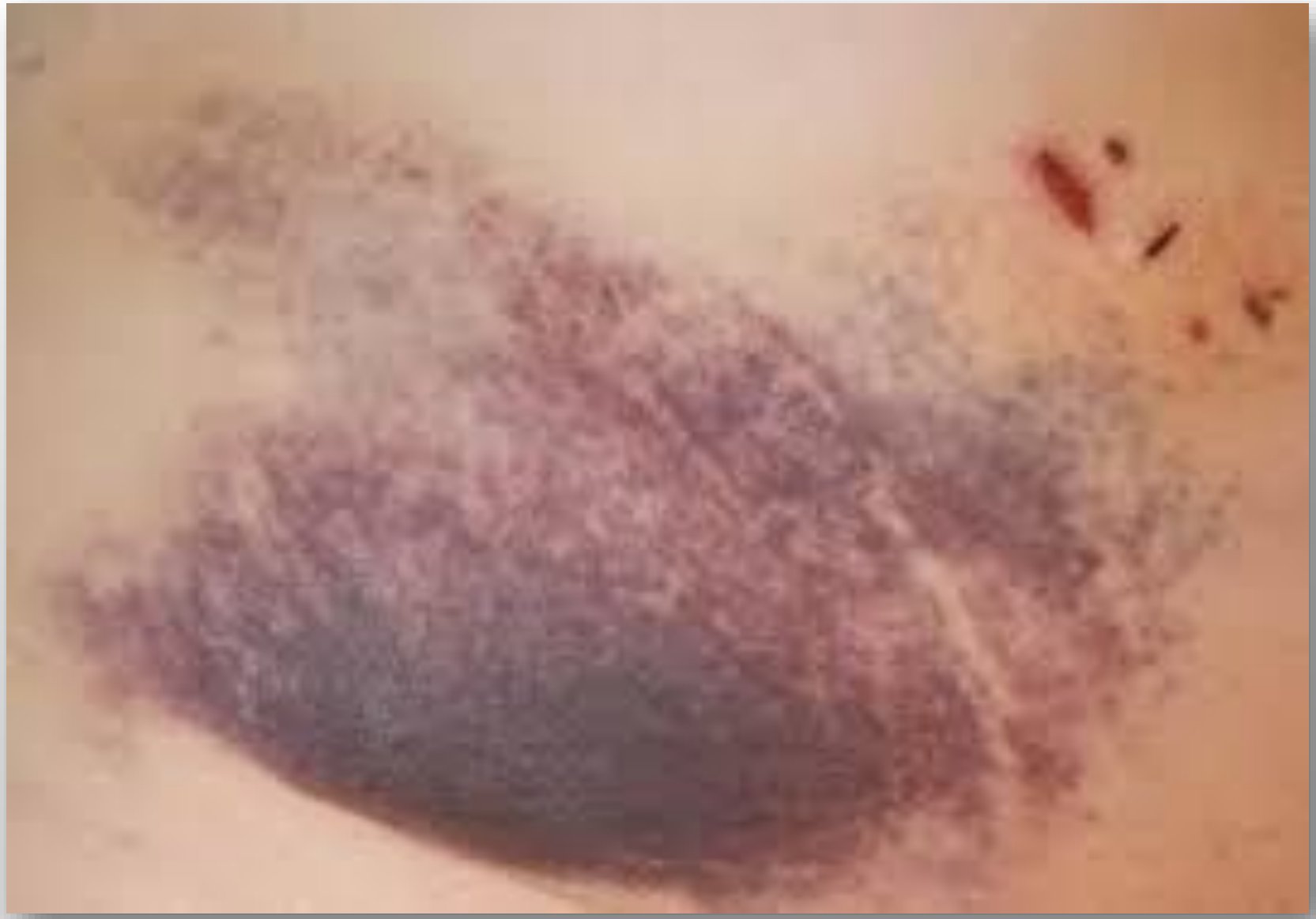
Bleeding disorders

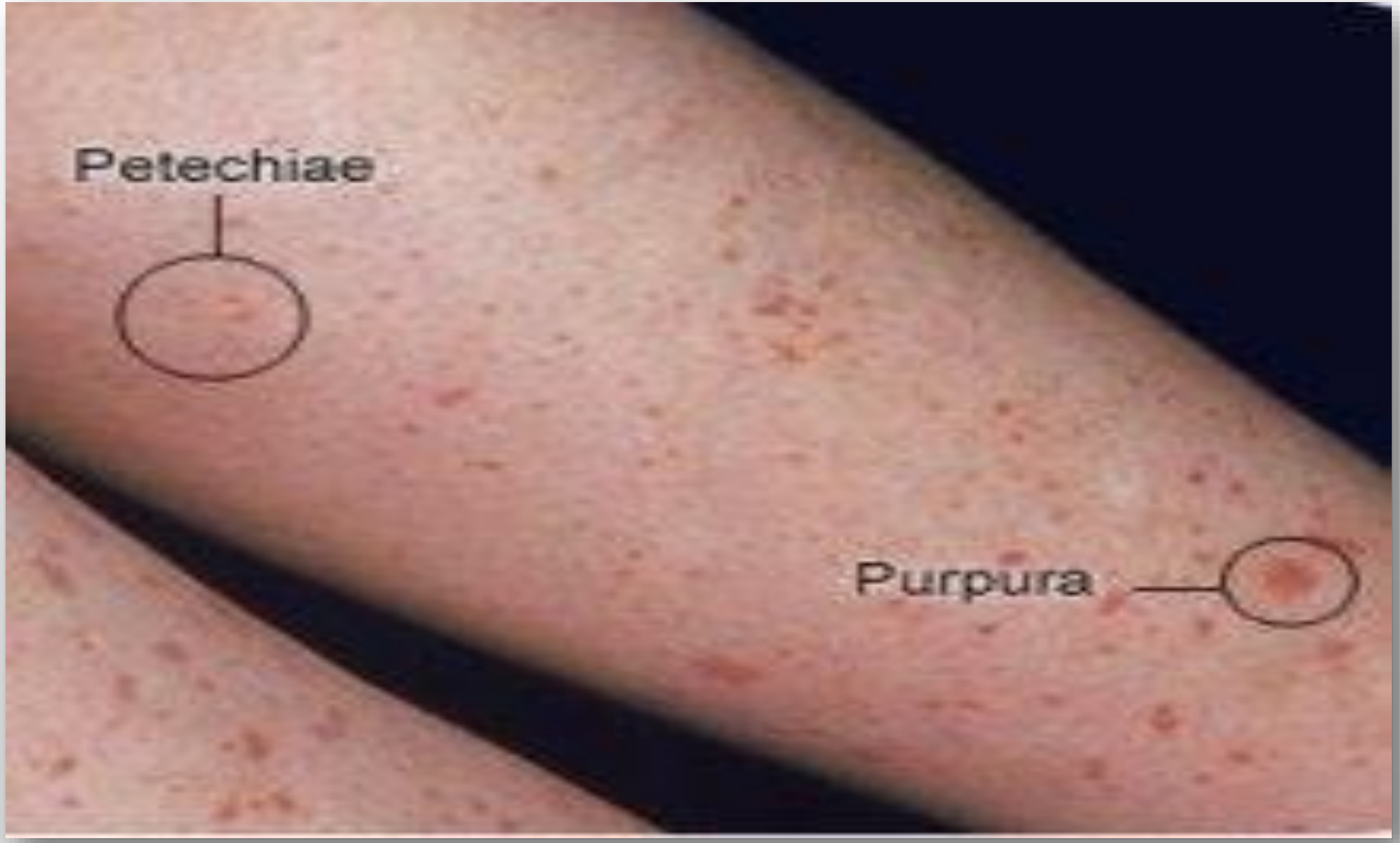
Afsheen Mahmood Noor

Learning Objectives:

1. Describe the role of Vit K in clotting
2. Describe the following bleeding disorders
   - Vitamin K deficiency
   - Thrombocytopenia
   - Hemophilia
   - Von Willebrand disease
3. Describe the effects of low platelet count on Hemostasis.
4. Define thrombus/thrombi
5. Define embolus/emboli
6. Enlist the causes of thromboembolic conditions
7. Describe Femoral venous thrombosis and its effects.






Petechiae
Purpura

Investigation of bleeding disorders

- ***Is there a generalized haemostatic defect?***
  - Multiple sites
  - Spontaneous bleeding.
  - Excessive bleeding after injury.
- ***Is the defect inherited or acquired?***
  - Family history of bleeding disorder should be sought.
- ***Is the bleeding suggestive of a vascular/platelet defect or a coagulation defect?***
  - Vascular/platelet bleeding.
  - Coagulation disorders

Bleeding

History

- Site of bleed
- Duration of bleed
- Precipitating causes, including previous surgery or trauma
- Family history
- Drug history
- Other medical conditions, e.g. liver disease

Examination

There are two major patterns of bleeding:

1. **Mucosal bleeding**

   Reduced number or function of platelets (e.g. bone marrow failure or aspirin) or von Willebrand factor (e.g. von Willebrand disease)

   - Skin: petechiae, bruises, post-surgical bleeding
   - Gum and mucous membrane bleeding
   - Fundal haemorrhage

2. **Coagulation factor deficiency**

   (e.g. haemophilia or warfarin)

   - Bleeding into joints (haemarthrosis) or muscles
   - Bleeding into soft tissues
   - Intracranial haemorrhage
   - Post-surgical bleeding

Bleeding disorders

- Vascular disorders
- Platelet disorders
- Inherited coagulation disorders
- Acquired coagulation disorders

24.3 Coagulation screening tests

Investigation	Normal range	Situations in which tests may be abnormal
Platelet count	150–400 × 10^9/L	Thrombocytopenia
Bleeding time	< 8 mins	Thrombocytopenia Abnormal platelet function von Willebrand disease Vascular and connective tissue abnormalities
Prothrombin time (PT)	9–12 secs	Deficiencies of factors II, V, VII or X Severe fibrinogen deficiency
Activated partial thromboplastin time (APTT)	26–36 secs	Deficiencies of factors II, V, VIII, IX, X, XI, XII Severe fibrinogen deficiency Unfractionated heparin therapy Antibodies against clotting factors Lupus anticoagulant
Fibrinogen concentration	1.5–4.0 g/L	Hypofibrinogenaemia, e.g. liver failure, disseminated intravascular coagulation

N.B. International normalised ratio (INR) is used only to monitor coumarin therapy and is not a coagulation screening test.

Vascular disorders/platelet disorders

- Characterized by easy bruising and spontaneous bleeding from small blood vessels.
- There is often bleeding into the skin.
  - Petechia/purpura.
- Bleeding from mucous membranes (esp. nose & mouth) occur but its rarely severe.
- Bleeding time (BT) is normal.
- causes

Table 8.22 Vascular disorders

Congenital

Hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu disease)
Connective tissue disorders (Ehlers–Danlos syndrome, osteogenesis imperfecta, pseudoxanthoma elasticum, Marfan's syndrome)

Acquired

Severe infections:
- Septicaemia
- Meningococcal infections
- Measles
- Typhoid

Allergic
- Henoch–Schönlein purpura
- Autoimmune rheumatic disorders (SLE, rheumatoid arthritis)

Drugs
- Steroids
- Sulphonamides

Others
- Senile purpura
- Easy bruising syndrome
- Scurvy
- Factitious purpura

Thrombocytopenia:

- Presence of very low platelets in peripheral blood.
- Bleeding due to thrombocytopenia or abnormal platelet function is characterized by purpura and bleeding from mucous membranes.
- Major haemorrhage is rare and is seen only in patients with severe thrombocytopenia.
- Easy bruising, purpura, epistaxis and menorrhagia are common.
- Physical examination is normal except for evidence of bleeding.

Immune thrombocytopenia

- Mechanism
- Clinical features
- Investigations p smear, B marrow,
- Treatment
- Steroid
- IV Ig/Anti Rh
- Splenectomy
- Immunosuppressive drugs (Azathioprin, Cyclophasphamide, Vinca alkaloids)

Table 8.24 Causes of thrombocytopenia

Impaired production
- Selective megakaryocyte depression:
  - Rare congenital defects
  - Drugs, chemicals and viruses
- As part of a general bone marrow failure:
  - Cytotoxic drugs and chemicals
  - Radiation
  - Megaloblastic anaemia
  - Leukaemia
- Myelodysplastic syndromes
- Myeloma
- Myelofibrosis
- Solid tumour infiltration
- Aplastic anaemia
- HIV infection

Excessive destruction or increased consumption
- Immune
- Autoimmune – ITP
- Drug induced, e.g. GP IIb/IIIa inhibitors, pencillins, thiazides
- Secondary immune (SLE, CLL, viruses, drugs, e.g. heparin, bivalirudin)
- Alloimmune neonatal thrombocytopenia
- Post-transfusion purpura
- Disseminated intravascular coagulation
- Thrombotic thrombocytopenic purpura

Sequestration
- Splenomegaly
- Hypersplenism

Dilutional
- Massive transfusion

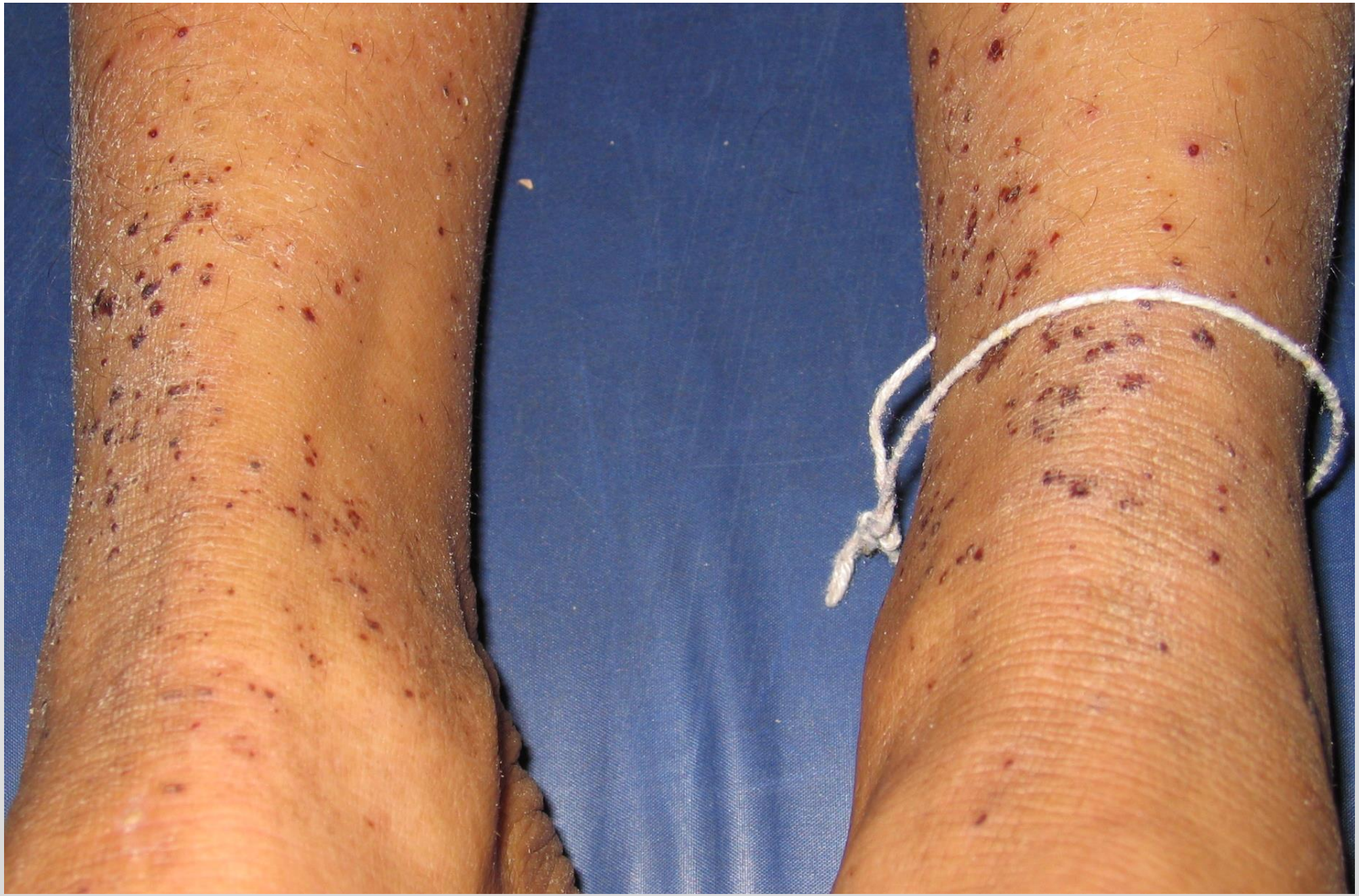


Table 8.23 Clinical effects caused by different levels of platelet count

Platelet count ($\times 10^9$/L)	Clinical defect
>500	Haemorrhage or thrombosis
500–100	No clinical effect
100–50	Moderate haemorrhage after injury
50–20	Purpura may occur Haemorrhage after injury
<20	Purpura common Spontaneous haemorrhage from mucous membranes Intracranial haemorrhage (rare)

From Colvin BT. *Medicine* 2004; 32(5):27–33, with permission from Elsevier.

Coagulation disorders:

- **Hereditary/inherited coagulation disorders:**
  - Sex linked (X chromosome)
    - Hemophilia A
    - Hemophilia B
  - Autosomal disorder
    - Von Willebrand disease
- **Acquired coagulation disorders:**
  - Vitamin K deficiency
  - Liver disease
  - Disseminated intravascular coagulation (DIC)
  - Excessive Fibrinolysis

Coagulation disorders

- May be inherited or acquired.
- Inherited are uncommon & usually involve one factor.
- Acquired ones occur more frequently
- Typically associated with bleeding after injury or surgery.
- In more severe forms, haemarthroses and muscle haematomas are formed.
- There is often a short delay between the precipitating event and overt hemorrhage or hematoma formation.

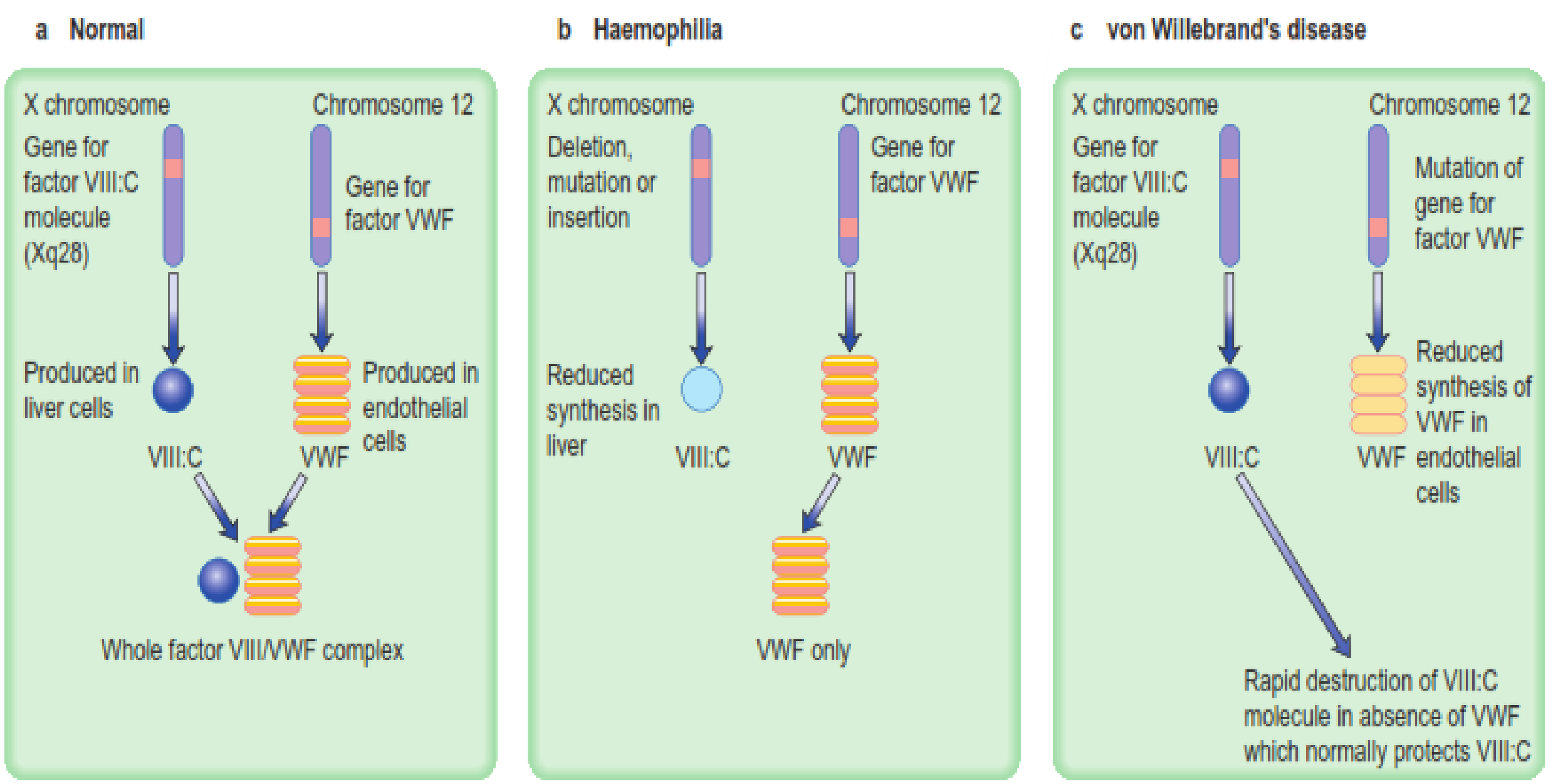


Figure 8.39 **(a)** Normal factor VIII synthesis. **(b)** Haemophilia A showing defective synthesis of factor VIIIc. **(c)** von Willebrand's disease showing reduced synthesis of VWF.

“The royal disease”

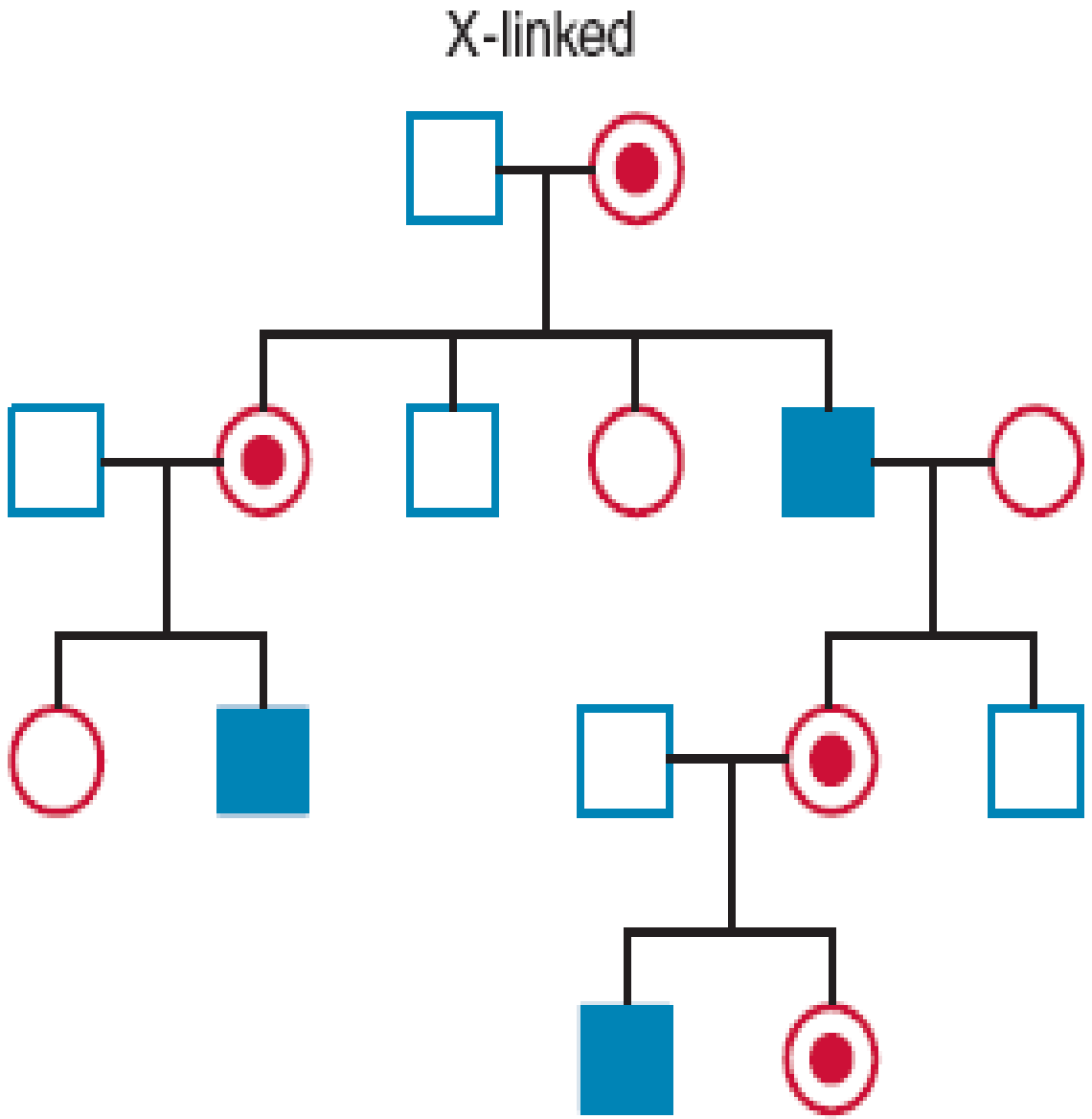
haemophilia became known as the “Royal disease” because it spread to the royal families of Europe through Victoria’s descendants

- Haemophilia appeared in Queen Victoria’s children, and through them spread into the royal families of Europe

- Hemophilia has been called a "royal disease". This is because the hemophilia *gene* was passed from Queen Victoria, who became Queen of England in 1837, to the ruling families of Russia, Spain, and Germany. Queen Victoria's gene for hemophilia was caused by spontaneous mutation.

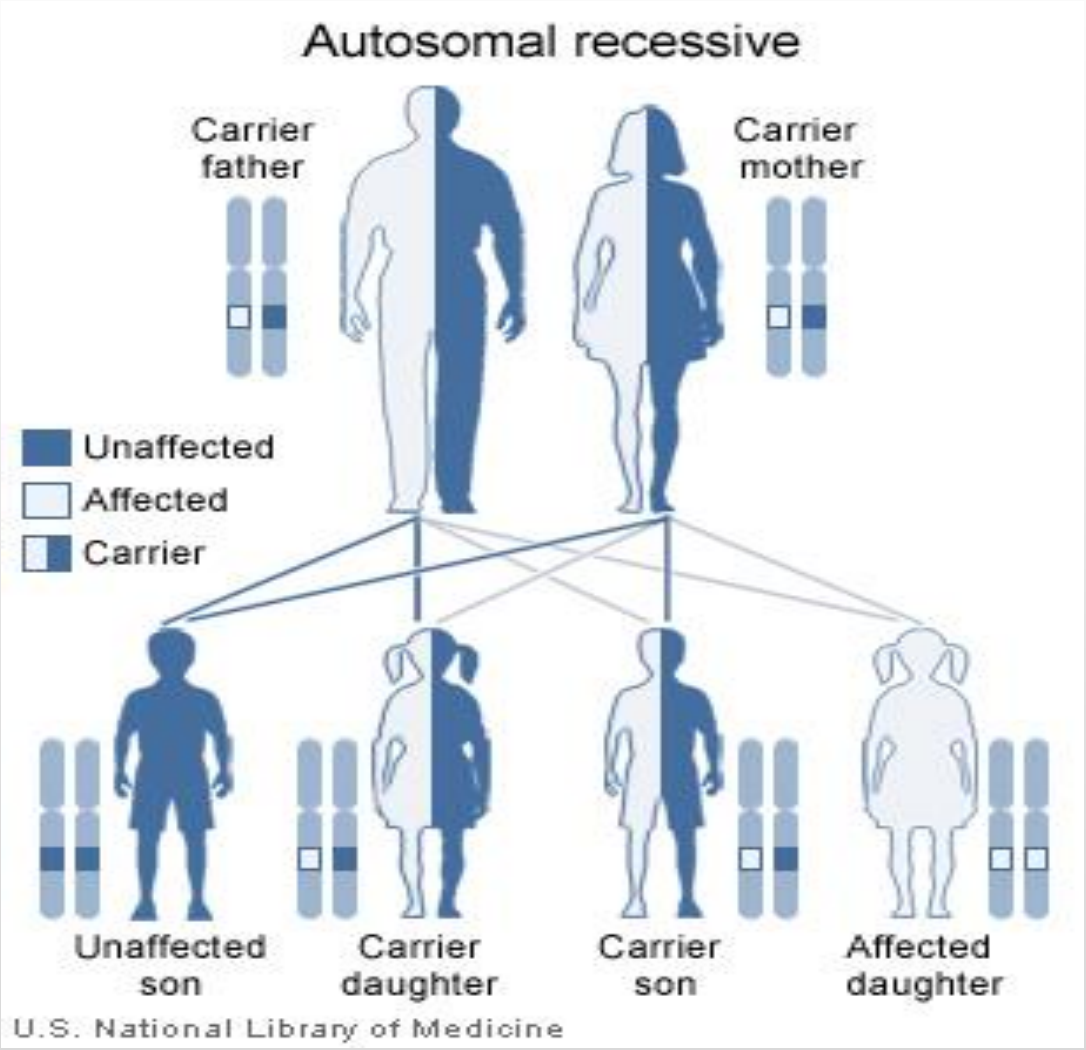
Hemophilia A

- Congenital deficiency of coagulation factor VIII.
- Prevalence of haemophilia A is about 1 in 5000 of the male population.
- It is inherited as an X-linked disorder.
- If a female carrier has a son, he has a 50% chance of having haemophilia, and a daughter has a 50% chance of being a carrier.
- All daughters of men with haemophilia are carriers and the sons are normal.


X-linked

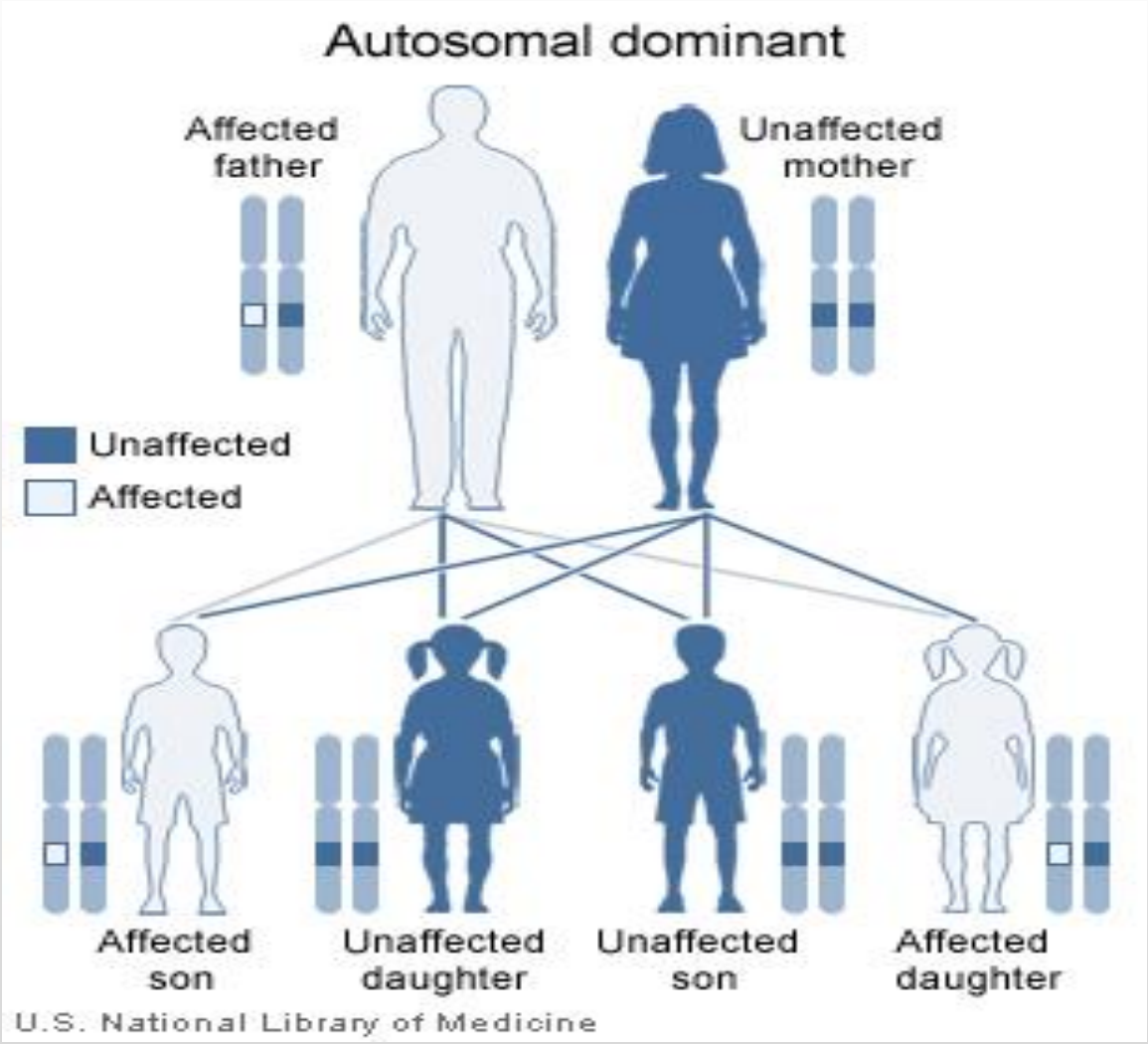
Autosomal recessive

- The disease appears in male and female children of unaffected parents.
- e.g., cystic fibrosis



Autosomal dominant

- Affected males and females appear in each generation of the pedigree.
- Affected mothers and fathers transmit the phenotype to both sons and daughters.
- e.g., Huntington disease.



Clinical feature

- Circumcision
- Joints
- Muscles
- Retro peritoneum

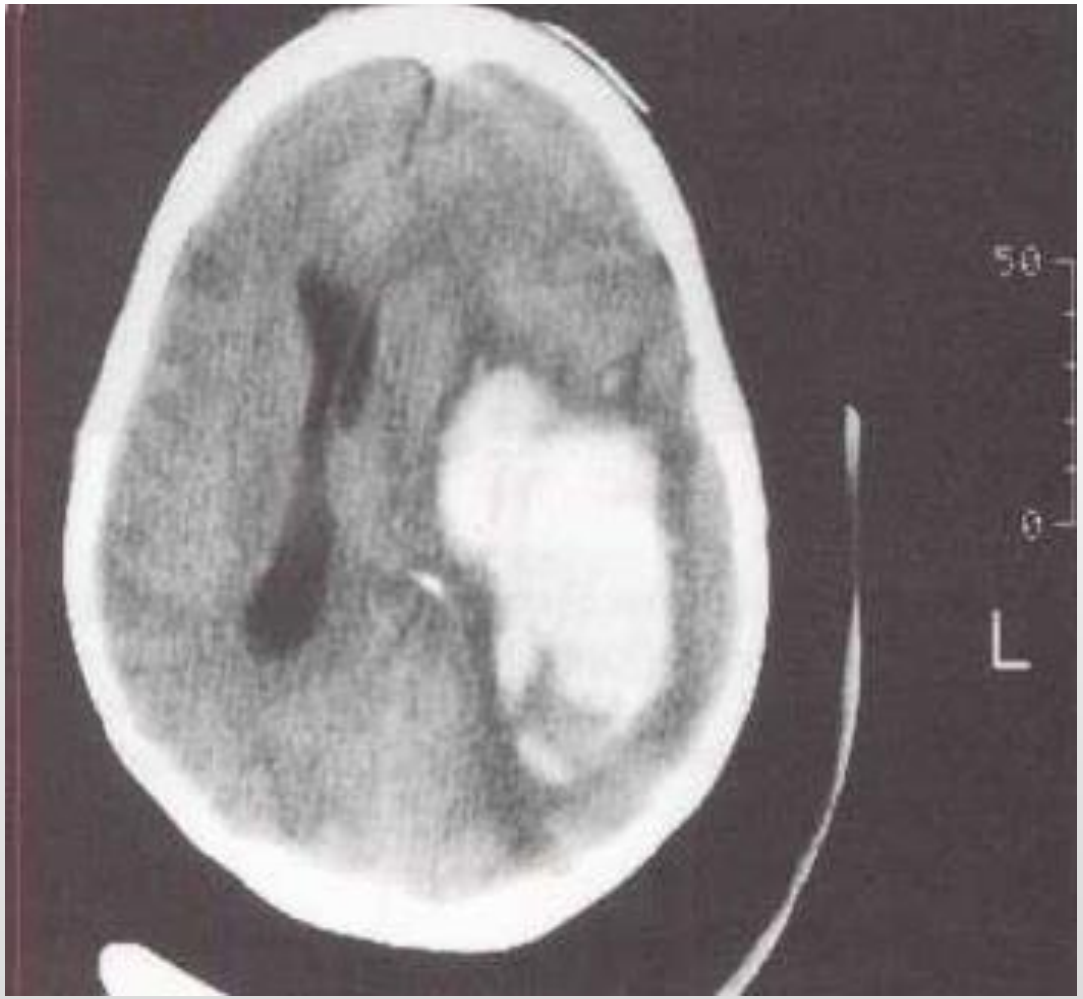

50
0
L

Table 11.20 Severity of haemophilia

Degree of severity	Factor VIII or IX level	Clinical presentation
Severe	<2%	Spontaneous haemarthroses and muscle haematomas
Moderate	2–10%	Mild trauma or surgery cause haematomas
Mild	10–50%	Major injury or surgery results in excess bleeding

Investigations

- BT
- CT
- APTT is prolonged
- PT is normal
- Factor VIIIC level....↓

Treatment

- Blood
- FFP
- Cryoprecipitate
- Factor VIII concentrate ever 12 hours
- DDAVP in mild cases
- Tranexamic acid adjuvant treatment in mucosal bleeding.
- Immunization HAV & HBV

Hemophilia B (Christmas disease)

- Factor IX deficiency
- Inheritance & clinical feature same as hemophilia A
- 1 in 30,000 males.
- No role of DDAVP
- Treated with factor IX concentrates.

Von Willebrand Disease

- Genetic disorder
  - (Type 1 & 2 dominant, type 3, recessive) caused by missing or defective von Willebrand factor (VWF), a clotting protein.
- VWF binds factor VIII, a key clotting protein, and platelets in blood vessel walls, which help form a platelet plug during the clotting process.
- Defective platelet function as well as factor VIII deficiency.
- Condition is named after Finnish physician Erik von Willebrand, who first described it in the 1920s.
- VWD is the most common bleeding disorder, affecting up to 1% of the US population.
- It is carried on chromosome 12 and occurs equally in men and women.

Von Willebrand Disease..... Cont

Signs & Symptoms

- Frequent nosebleeds, bleeding gums.
- Easy bruising and excessive bleeding during & after invasive procedures, such as tooth extractions and surgery.
- Women often experience heavy menstrual bleeding and hemorrhaging after childbirth.

Von willebrand's disease

- Gene on 12, autosomal. Type 1,2,3
- VWF is produced by endothelial cells & megakaryocytes
- Clinical feature
- Management with DDAVP, VWF

Table 8.25 **Blood changes in haemophilia A, von Willebrand's disease and vitamin K deficiency**

	Haemophilia A	von Willebrand's disease	Vitamin K deficiency
Bleeding time	Normal	↑	Normal
PT	Normal	Normal	↑
APTT	↑+	↑±	↑
VIII: C	↓++	↓	Normal
VWF	Normal	↓	Normal

Vitamin K deficiency:

- Vitamin K is necessary for the ɣ Carboxylation of Glutamic acid residues on coagulation factors 2,7,9,10, protein C & S.
- Deficiency of Vitamin K maybe due to:
  - Inadequate stores.
    - as in hemorrhagic disease of the new born
    - Little vitamin K in breast milk
    - No hepatic stores
  - Liver disease.
  - Malabsorption of vitamin K.
  - Oral anticoagulant drugs.

Vitamin K.....

- Investigations:
- Platelets.....?
- PT/APTT.....?
- BT.....?
- BT.....N
- PT/APTT.....↑
- Platelets.....Normal

Liver disease:

- Vitamin K deficiency
- Reduced synthesis
- Thrombocytopenia
- Functional abnormalities
- Disseminated intravascular coagulation

Thromboembolic conditions:

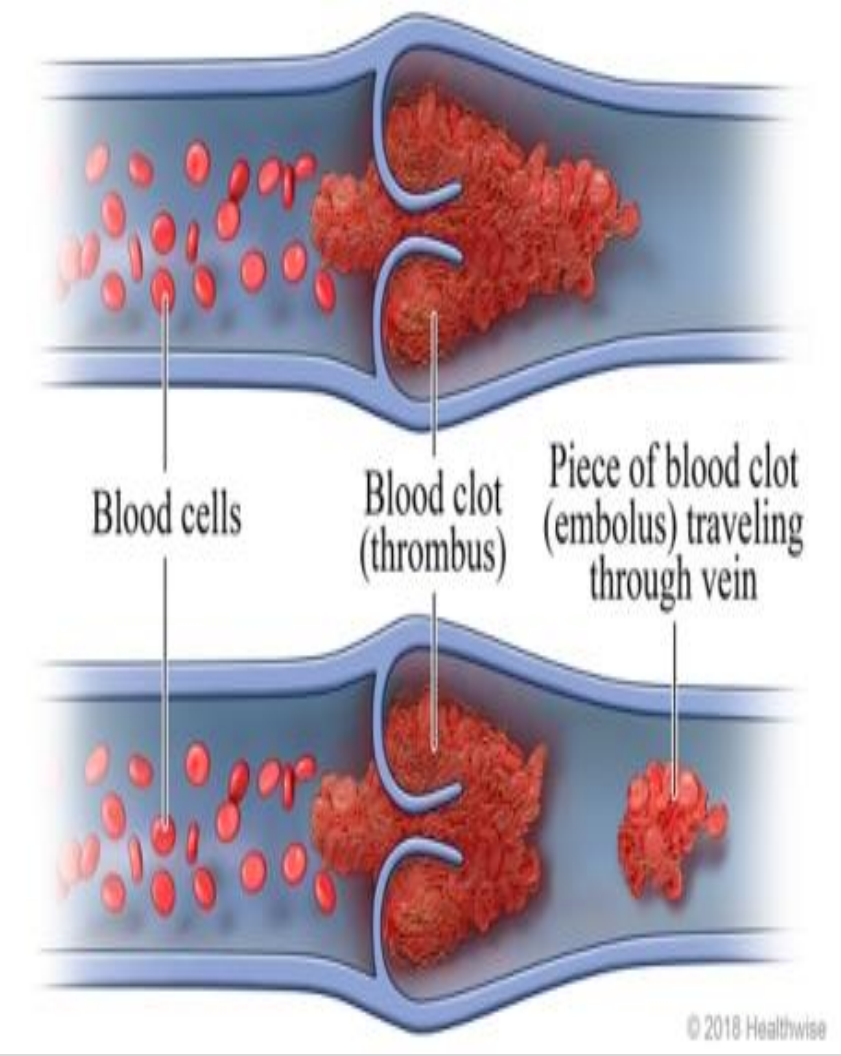
A *thrombus* is defined as a solid mass formed in the circulation from the constituents of the blood during life.

An abnormal clot that develops in a blood vessel is called a *thrombus*.

Emboli:

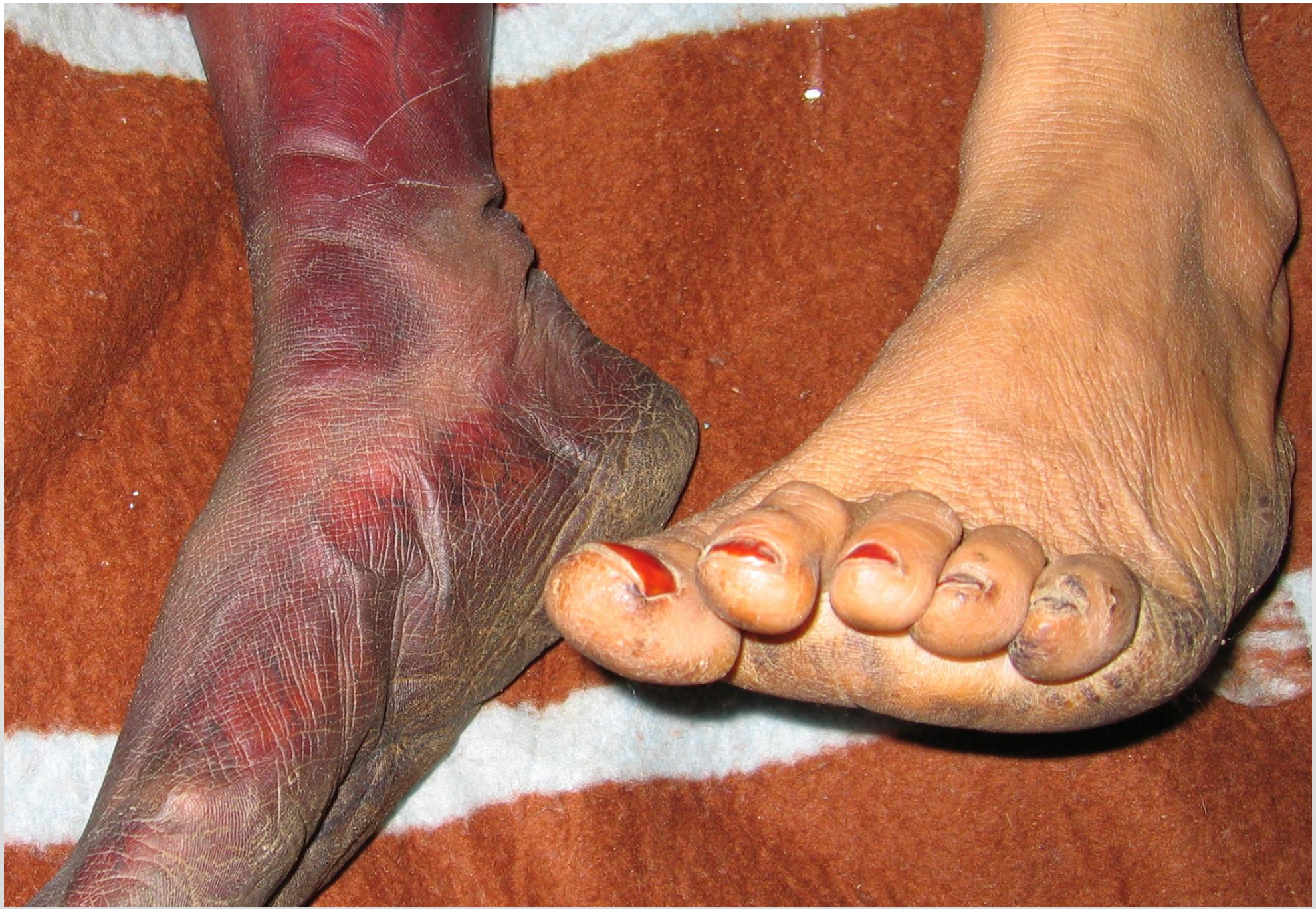
- Once a clot has developed, continued flow of blood past the clot is likely to break it away from its attachment and cause the clot to flow with the blood; such freely flowing clots are known as ***emboli***.

- Types:
  - Arterial
  - Venous



Arterial

- Usually atheromatous lesion, cardiac valves, post MI
- Thrombus is usually a white one
- Risk factors (all risk factors for atheroma, all risk factors for AF & aneurysm)
- Clinical features
- Management onset of action collaterals which type of vital organ is involved



Venous risk factors

Box 10.2 Risk factors for venous thrombosis

Environmental

- Immobility
- Surgery, trauma
- Pregnancy, puerperium
- Long distance travel
- Use of combined oral contraceptives

Inherited

- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Factor V Leiden (activated protein C resistance, APCR)
- Prothrombin PT20210A allele

Acquired

- Antiphospholipid antibody, lupus anticoagulant
- Hyperhomocysteinaemia
- Malignancy
- Myeloproliferative diseases

Pathophysiology of thromboembolic conditions:

1. A roughened endothelial surface of a vessel—as may be caused by arteriosclerosis, infection, or trauma—is likely to initiate the clotting process.

2. Blood often clots when it flows very slowly through blood vessels, where small quantities of thrombin and other procoagulants are always being formed.

Disseminated intravascular coagulation (DIC)

- Widespread generation of fibrin within blood vessels, owing to activation of coagulation by release of procoagulant material, and by diffuse endothelial damage or generalized platelet aggregation.

Box 8.5 Causes of DIC

- Malignant disease
- Septicaemia (e.g. Gram-negative including meningococcal)
- Haemolytic transfusion reactions
- Obstetric causes (e.g. abruptio placentae, amniotic fluid embolism, pre-eclampsia)
- Trauma, burns, surgery
- Other infections (e.g. falciparum malaria)
- Liver disease
- Snake bite

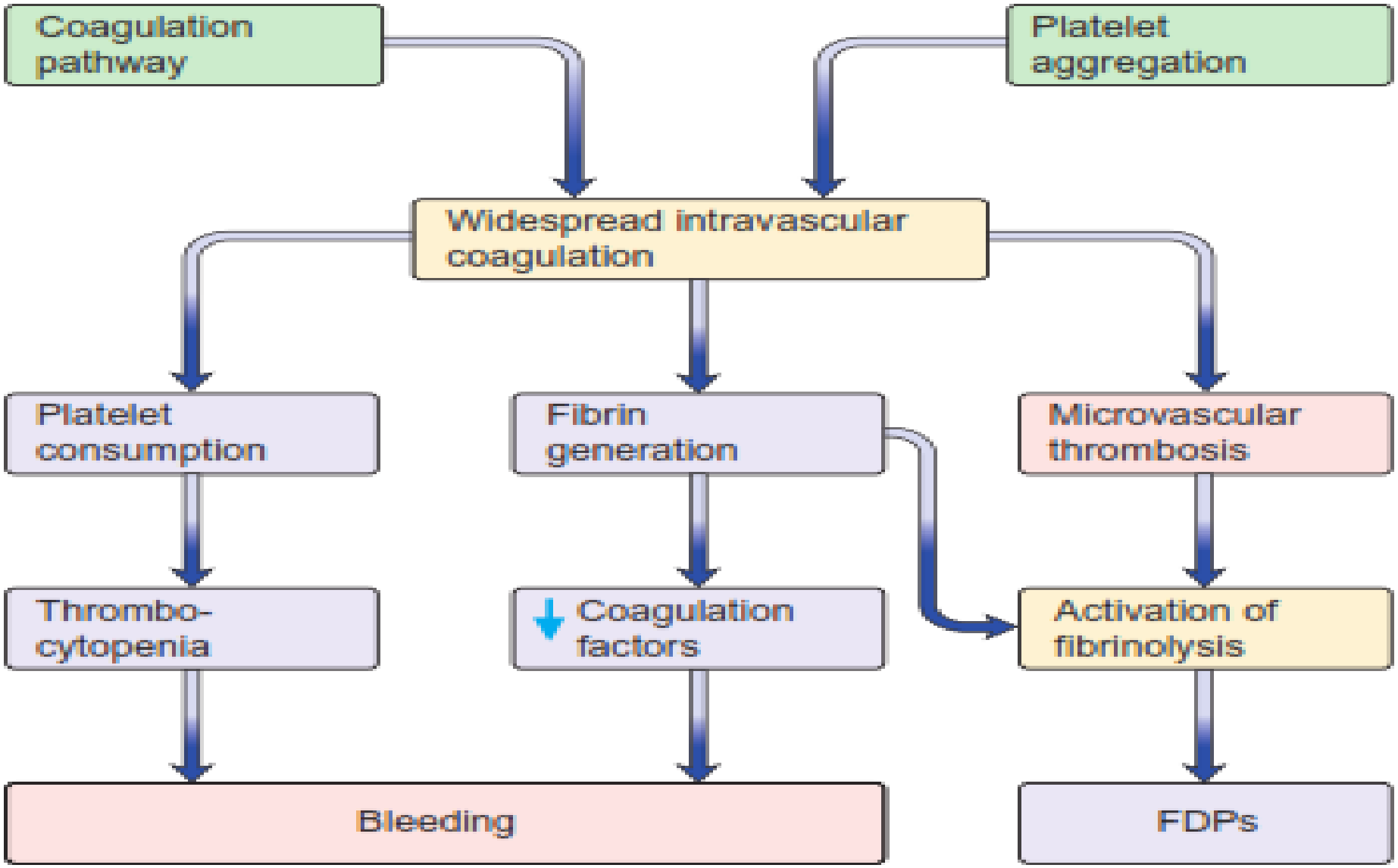


Figure 8.40 Disseminated intravascular coagulation.
FDPs, fibrin degradation products.

Clinical features:

- The underlying condition is usually obvious.
- Patient is often acutely ill and shocked.
- The clinical presentation of DIC varies from no bleeding at all to profound haemostatic failure with widespread haemorrhage.
- Bleeding may occur from the mouth, nose and venepuncture sites and there may be widespread ecchymoses.

Investigations:

- ***Severe cases with haemorrhage:***
  - The PT, APTT and TT are usually very prolonged, and the fibrinogen level markedly reduced.
  - High levels of FDPs, including D-dimer, are found owing to the intense fibrinolytic activity stimulated by the presence of fibrin in the circulation.
  - There is severe thrombocytopenia.
  - The blood film may show fragmented red blood cells.

- ***Mild cases without bleeding:***
  - Increased synthesis of coagulation factors and platelets
  - Normal PT, APTT, TT and platelet counts
  - FDPs are raised.

Postural hypotension/Orthostatic hypotension

- When autonomic reflexes are impaired or intravascular volume is markedly depleted, a significant reduction in blood pressure occurs upon standing, a phenomenon termed **"orthostatic hypotension.“**

- Postural (orthostatic) hypotension is diagnosed when, within two to five minutes of quiet standing (after a five-minute period of supine rest), one or both of the following is present:

- At least a 20 mmHg fall in systolic pressure

- At least a 10 mmHg fall in diastolic pressure

Causes:

Many disorders can cause orthostatic hypotension:

- with the major mechanisms being autonomic dysfunction affecting the baroreflex,
- severe volume depletion, and
- adverse effects of medications

References

1. Guyton and Hall Textbook of Medical Physiology (Guyton Physiology) 13th Edition.
2. Human Physiology: From Cells to Systems (Lauralee Sherwood)
3. Essentials of Kumar and Clark's Clinical Medicine E-Book. Elsevier Health Sciences; 8th Edition.
4. Google images.
5. https://www.youtube.com/watch?v=uS1RGbW8UbQ