

Bleeding disorders

TUCOM

Dep. of Medicine

5th year

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Bleeding disorders

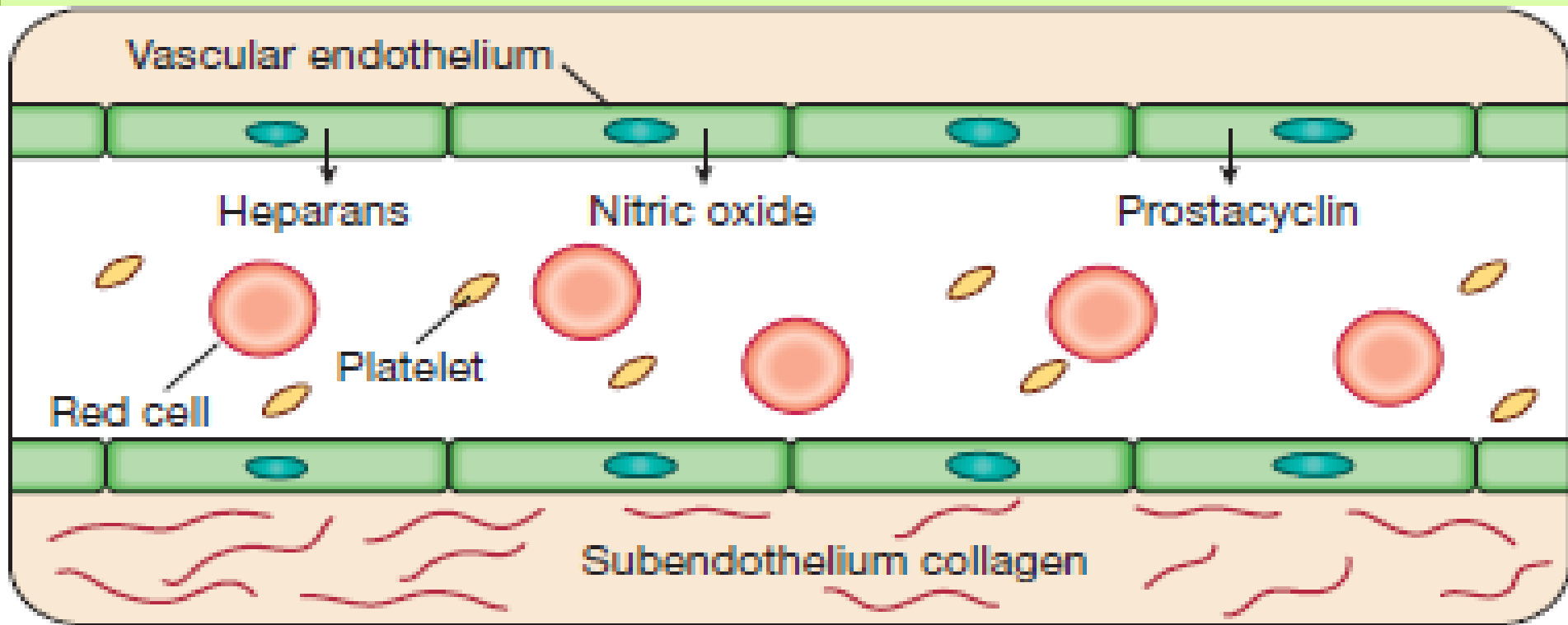
1. Define haemostasis
2. Explain the stages haemostasis
3. Enumerate the causes bleeding disorders
4. Clarify the clinical assessment of patient with bleeding disorders
5. Outline the investigations of bleeding disorders
6. Discuss the following conditions: Hereditary haemorrhagic telangiectasia, Inherited coagulation disorders and Von Willebrand disease.
7. Review the acquired bleeding disorders
8. Outline the management of bleeding disorders

Haemostasis

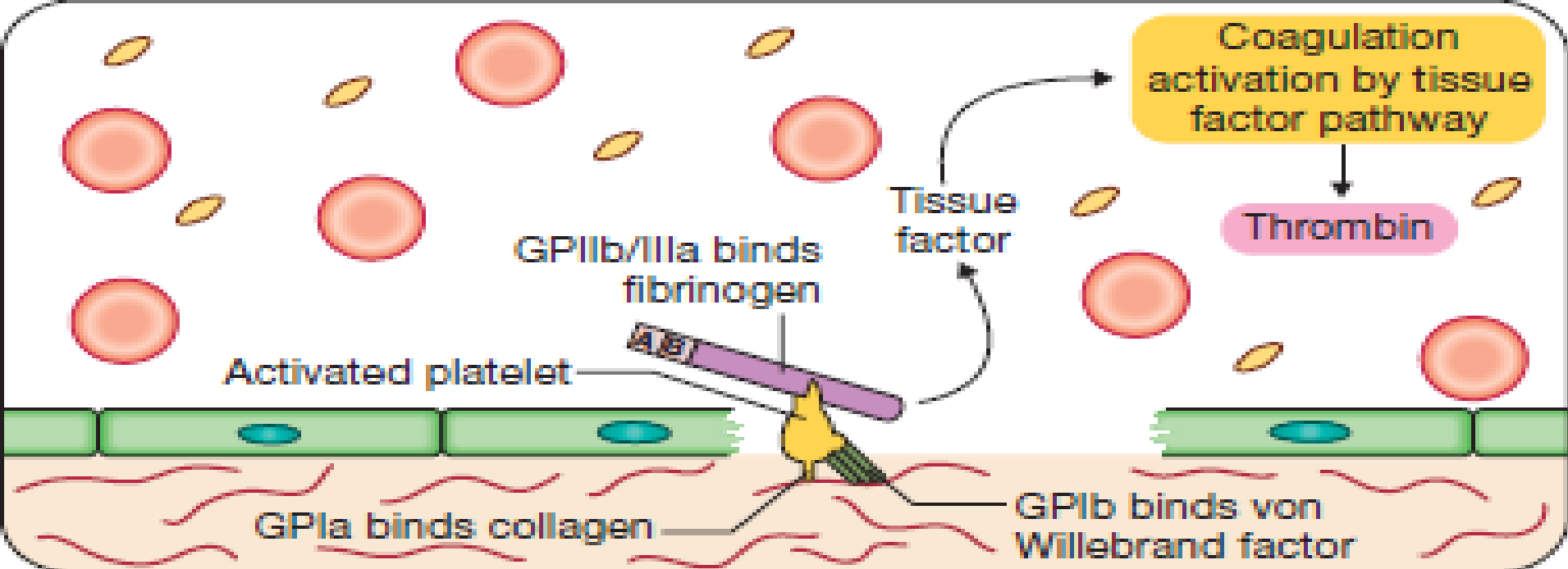
Haemostasis is the physiologic balance of procoagulant and anticoagulant forces that maintain both liquid blood flow and the structural integrity of the vasculature, but must be able to form a localized clot at the site of vascular injury in order to prevent excessive bleeding.

This is achieved by complex interactions between the vascular endothelium, platelets, coagulation factors, natural anticoagulants and fibrinolytic enzymes. Dysfunction of any of these components may result in haemorrhage or thrombosis.

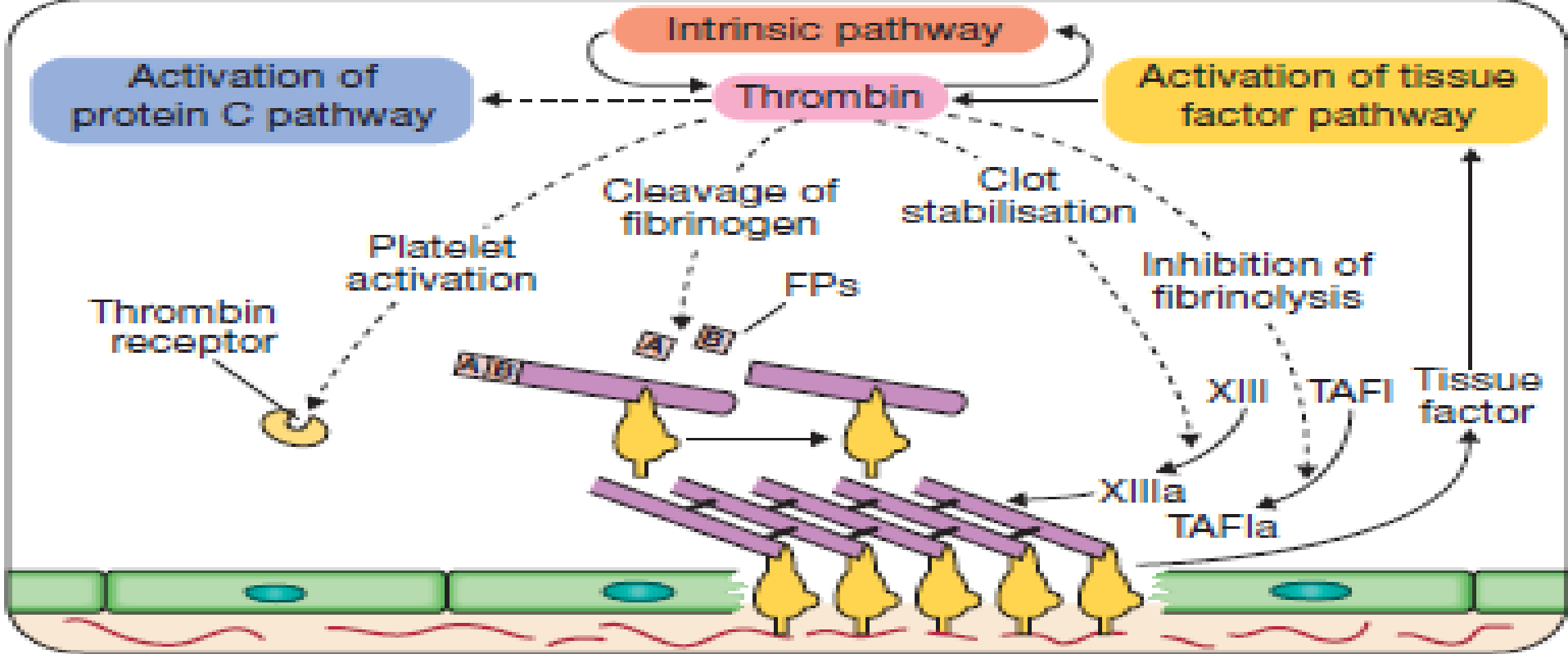
The stages of normal haemostasis



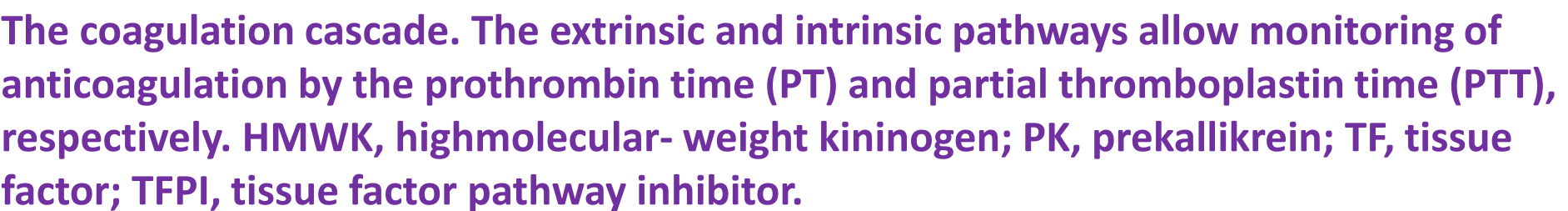
Stage 1 Pre-injury conditions encourage flow. The vascular endothelium produces substances (including nitric oxide, prostacyclin and heparans) to prevent adhesion of platelets and white cells to the vessel wall. Platelets and coagulation factors circulate in a non-activated state.



Stage 2 Early haemostatic response: platelets adhere, coagulation is activated. At the site of injury, the endothelium is breached, exposing subendothelial collagen. Small amounts of tissue factor (TF) are released. Platelets bind by specific receptors (GPIb and GPIIb/IIIa) to von Willebrand factor and fibrinogen, respectively. Coagulation is activated by the tissue factor (extrinsic) pathway, generating small amounts of thrombin.

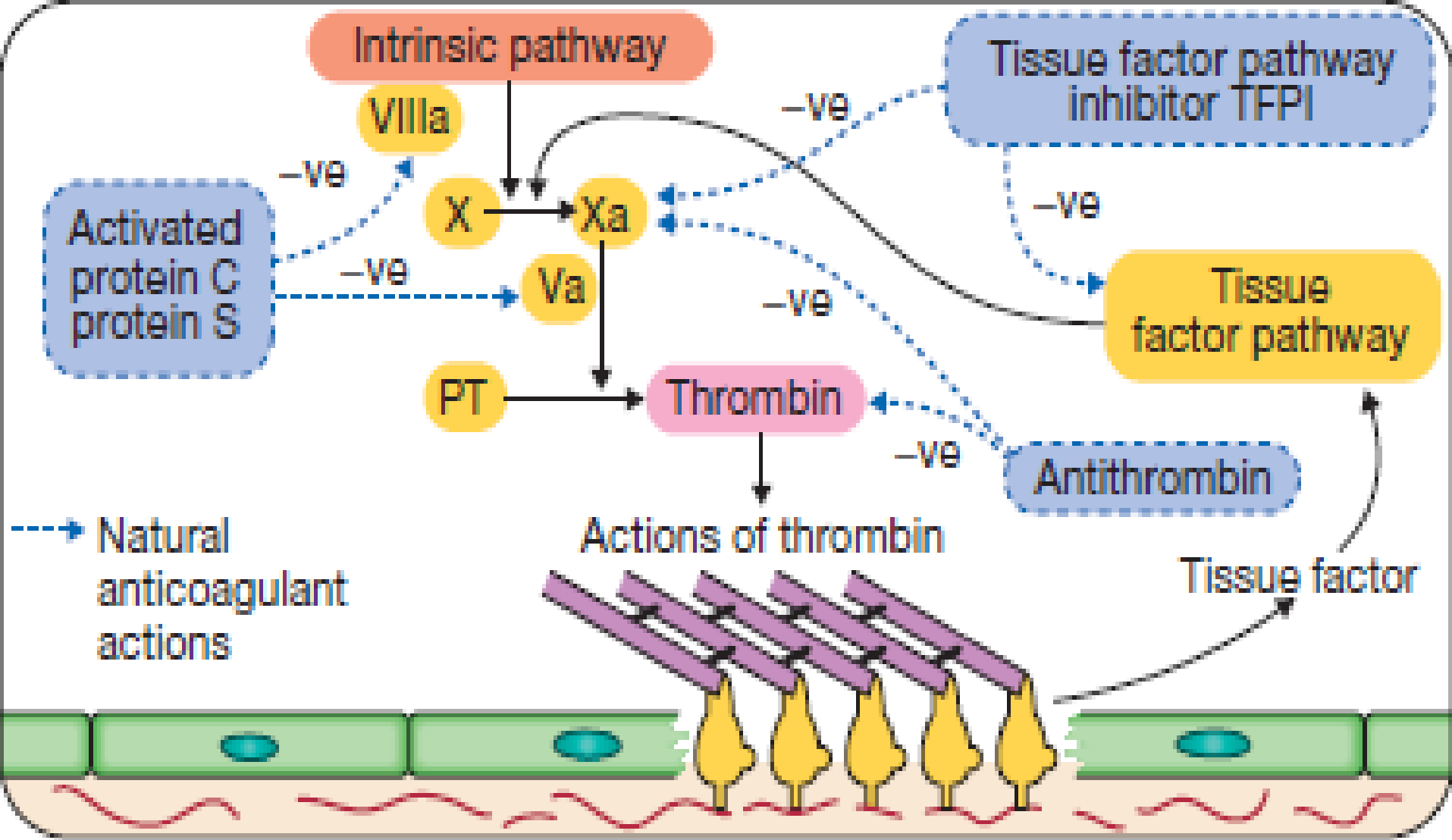


Stage 3 Fibrin clot formation: platelets become activated and aggregate results in release of the platelet granule contents, enhancing coagulation further. Thrombin plays a key role in the control of coagulation: the small amount generated via the TF pathway, the 'intrinsic' pathway becomes activated and large amounts of thrombin are generated. Thrombin directly causes clot formation. Fibrin monomers are cross-linked by factor XIII, which is also activated by thrombin. Having had a key role in clot formation and stabilisation.

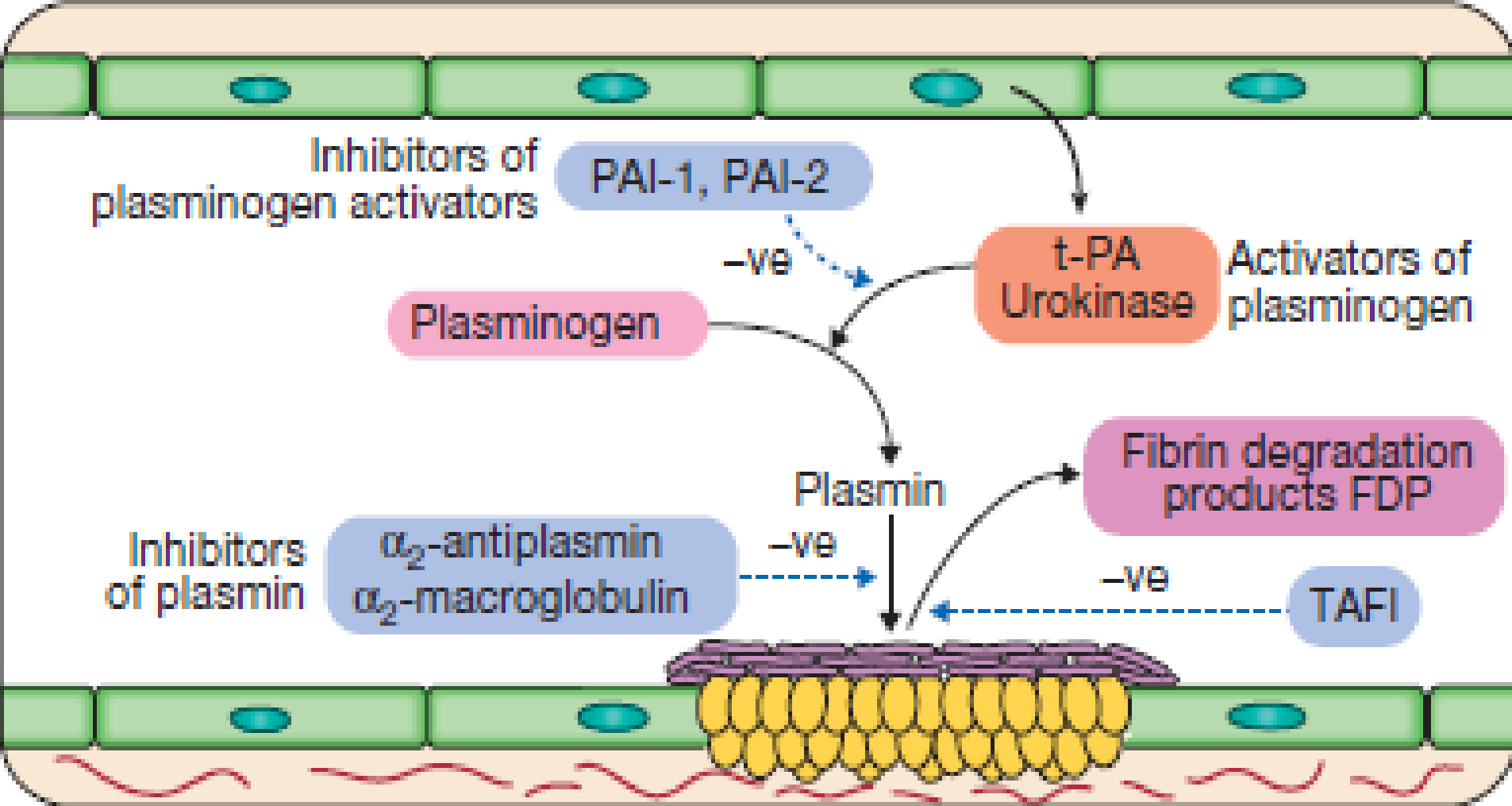


The coagulation factors:

- **I: Fibrinogen**
 - **II: Thrombin**
 - **III: Tissue factor**
 - **IV: Ca⁺⁺**
 - **V: Proaccerin / Labile factor**
 - **VI: No longer used**
 - **VII: Proconvertin**
 - **VIII: Antihemophilic factor (AHF)**
 - **IX: Christmas F/ Antihemophilic factor B**
 - **X: Stuart factor**
 - **XI: Plasma thromboplastin antecedent (PTA)/ antihemophilic factor C**
 - **XII: Hageman factor**
 - **XIII: Fibrin stabilisig factor**
- **All produce by the liver. Fact. V and VIII produce also by platelets and endothelial Cells.**
 - **VIT. K dependent factors: II, VII, IX and X (inhibited by warfarin)**



Stage 4 Limiting clot formation: natural anticoagulants reverse activation of coagulation factors. Once haemostasis has been secured, the propagation of clot is curtailed by anticoagulants: Antithrombin, protein C (PC) and protein S (PS).



Stage 5 Fibrinolysis: plasmin degrades fibrin to allow vessel recanalisation and tissue repair. Plasmin, the main fibrinolytic enzyme, is produced when plasminogen is activated, e.g. by tissue plasminogen activator (t-PA) or urokinase in the clot. Plasmin hydrolyses the fibrin clot, producing fibrin degradation products, including the D-dimer.

Bleeding disorders

Normal bleeding is seen following surgery and trauma.

Pathological bleeding occurs when structurally abnormal vessels rupture or a defect in haemostasis.

Causes:

1- Vascular Causes: vasculitis, senile purpura, scurvy or vitamin C deficiency, hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome), pseudoxanthoma elasticum and Ehlers Danlos syndrome.

2- Deficiency or dysfunction of platelets

3- Coagulation factors disorders

4- Von Willebrand disease

5- Drugs: excessive antiplatelets, anticoagulant and fibrinolytic drugs.

Clinical assessment

It is important to consider the following:

1- Site of bleeding:

- Bleeding into muscle and joints, along with retroperitoneal and intracranial haemorrhage, indicates a likely defect in coagulation factors.
- Petechiae, purpura, ecchymoses, prolonged bleeding from superficial cuts, epistaxis and gastrointestinal haemorrhage indicates thrombocytopenia, a platelet function disorder or von Willebrand disease.
- Recurrent bleeds at a single site suggest a local structural abnormality.

2- Duration of history: to assess whether the disorder is congenital or acquired.

3- Precipitating causes: Bleeding arising spontaneously indicates a more severe defect than bleeding that occurs only after trauma.

4- Surgery: Ask about operations.

- Dental extractions, tonsillectomy and circumcision are stressful tests of the haemostatic system.
- Immediate post-surgical bleeding suggests defective platelet plug formation and primary haemostasis
- Delayed haemorrhage is more suggestive of a coagulation defect.
- In postsurgical patients, persistent bleeding from a single site is more likely to indicate surgical bleeding than a bleeding disorder.

5- Drugs: Use of antiplatelets, anticoagulant and fibrinolytic drugs must be elicited.

6- Family history: a positive family history may indicate inherited disorders, like haemophilias or deficiencies of factor VII, X and XIII, which are recessively inherited.

Examination

- Petechiae, purpura and ecchymosis, in the skin, mucous membranes, or in the gastrointestinal tract tends to occur more often in patients with thrombocytopenia, qualitative platelet defects, vascular abnormalities, and von Willebrand disease (vWD). Palpable purpura occurs in vasculitis.
- Bleeding in deep organs; joints, or muscles or retroperitoneal space is more commonly associated with factor deficiencies, such as hemophilia.
- Telangiectasia of lips and tongue points to hereditary haemorrhagic telangiectasia.
- Underlying associated systemic illness such as a haematological or other malignancy, liver disease, renal failure, connective tissue disease.



24.3 Coagulation screening tests

Investigation	Reference range*	Situations in which tests may be abnormal
Platelet count	150–400 $\times 10^9/L$	Thrombocytopenia
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, DIC

Vessel wall abnormalities

1. Congenital, such as hereditary haemorrhagic telangiectasia
2. Acquired, as in a vasculitis or scurvy

Hereditary haemorrhagic telangiectasia (HHT) or Osler-Weber- Rendu syndrome

It is an autosomal dominant inherited condition

Telangiectasia and small aneurysms are found on the fingertips, face and tongue, and in the nasal passages, lung and gastrointestinal tract.

large pulmonary arteriovenous malformations (PAVMs) that cause arterial hypoxaemia due to a right-to-left shunt. These predispose to paradoxical embolism, resulting in stroke or cerebral abscess.

Patients present either with recurrent bleeds, particularly epistaxis, or with iron deficiency due to occult GI bleeding.

Treatment:

- Can be difficult because of the multiple bleeding points
- Regular iron therapy often allows the marrow to compensate for blood loss.
- Local cautery or laser therapy may prevent single lesions from bleeding.

Platelet disorders (previous lecture)



Coagulation disorders

- **Congenital:** X-linked like Haemophilia A and B. Autosomal like Von Willebrand disease
- **Acquired:** may be due to under-production (e.g. in liver failure), increased consumption (e.g. in disseminated intravascular coagulation) or inhibition of function such as heparin therapy or inhibition of synthesis such as warfarin therapy.

Inherited bleeding disorders

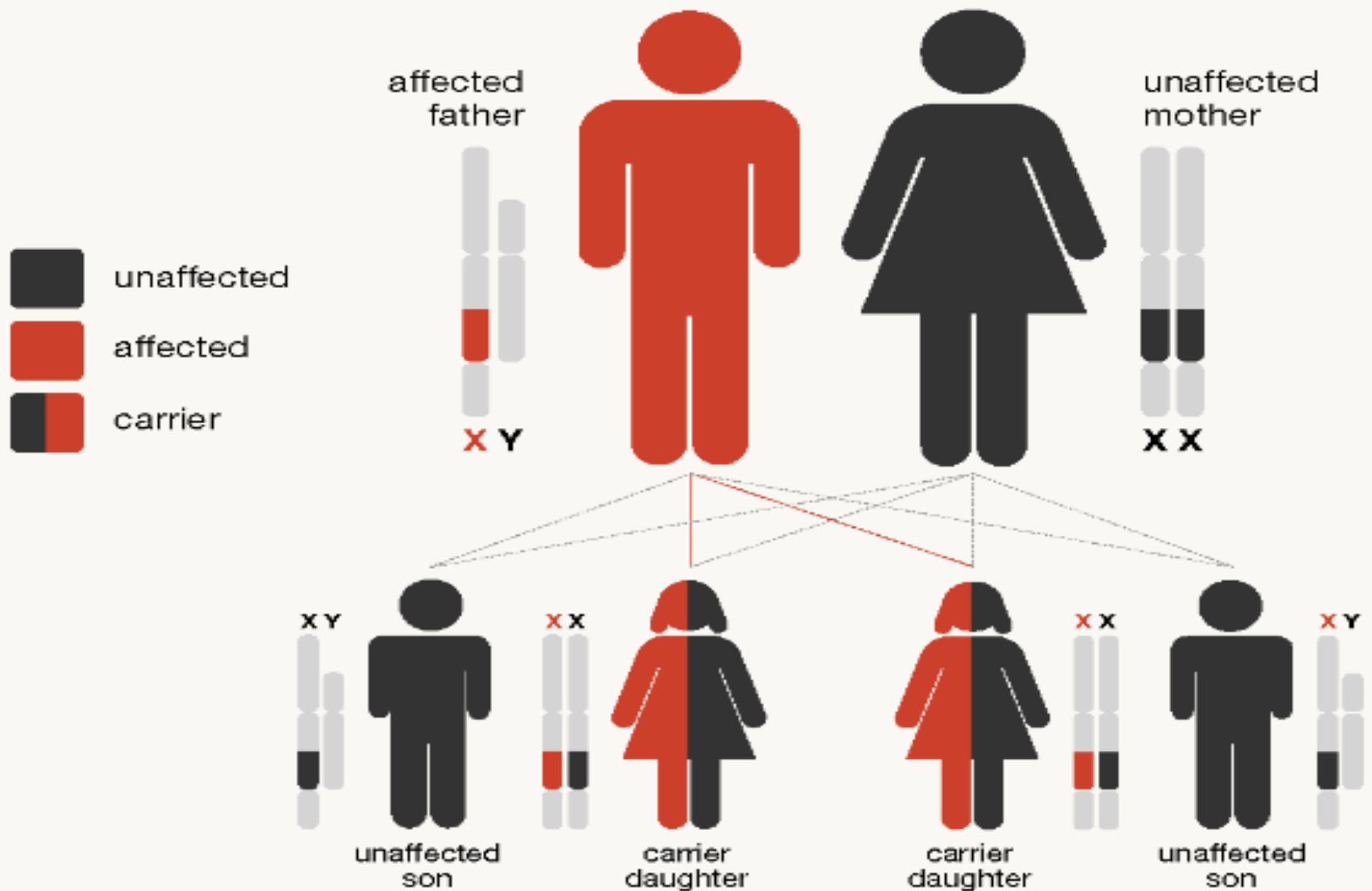
Haemophilia A

Factor VIII deficiency resulting in haemophilia A affects 1/10 000 individuals. It is the most common congenital coagulation factor deficiency. Factor VIII is primarily synthesised by the liver and endothelial cells, and has a half-life of about 12 hours. It is protected from proteolysis in the circulation by binding to von Willebrand factor (vWF).

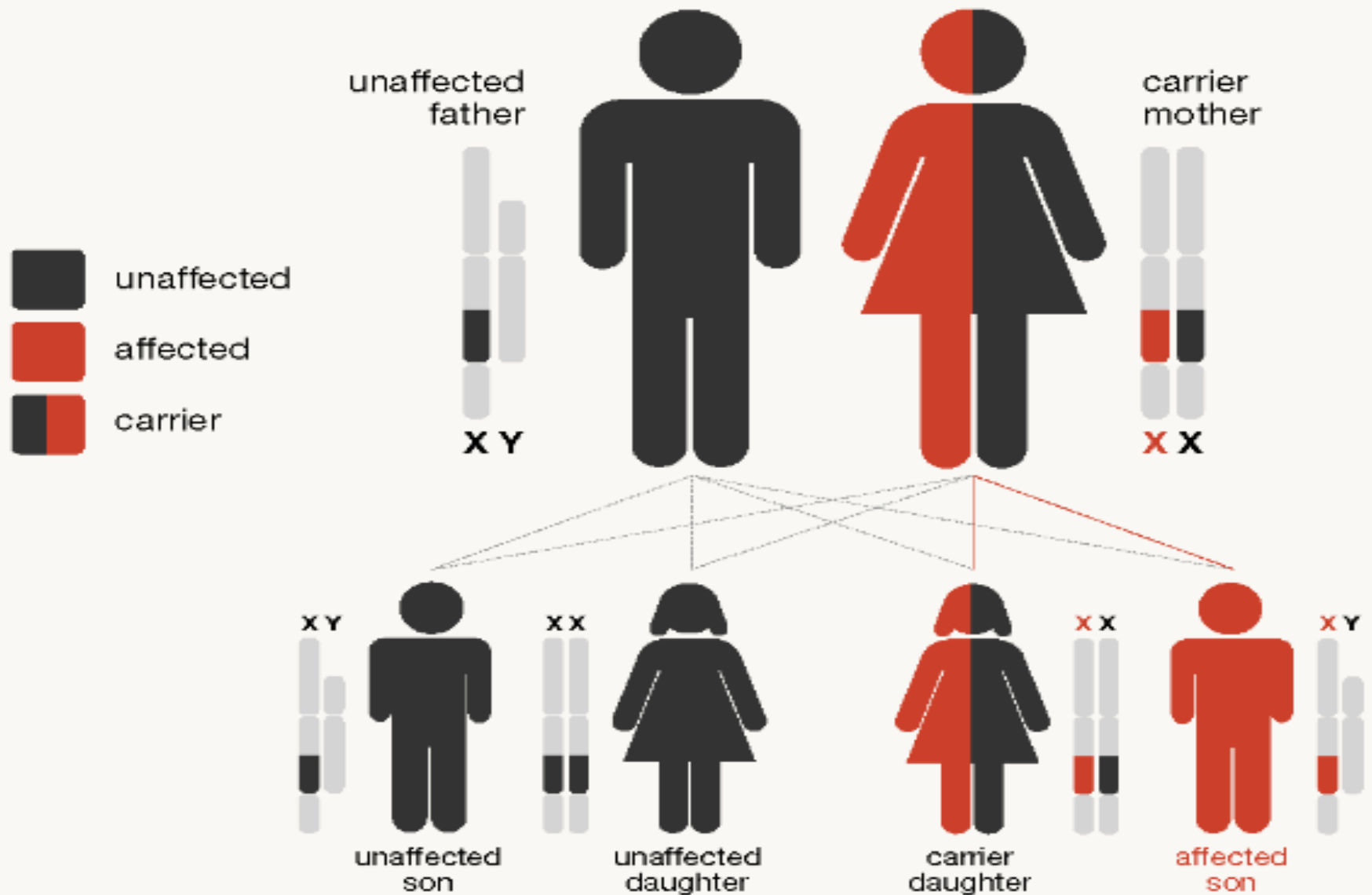
Genetics

It is X-linked recessive disease. Thus all daughters of haemophiliacs are obligate carriers and they, in turn, have a 1 in 4 chance of each pregnancy resulting in the birth of an affected male.

All family members have the same factor VIII gene mutation and a similarly severe or mild phenotype.



Inheritance of haemophilia in the case of an affected father and a mother who is not a haemophilia carrier.



Inheritance of haemophilia in the case of a 'carrier' mother (with one copy of the haemophilia gene) and a father without haemophilia

Clinical features

C/F closely related to residual factor VIII levels:

- Severe haemophilia (< 1% of normal factor VIII levels) present with spontaneous bleeding into skin, muscle and joints. Retroperitoneal and intracranial bleeding is also a feature. Babies with severe haemophilia have an increased risk of intracranial haemorrhage.
- Moderate and mild haemophilia (factor VIII levels 1–40%) present with the same pattern of bleeding, but usually after trauma or surgery.

Bleeding is typically into large joints, especially knees, elbows, ankles and hips. Muscle haematomas are also characteristic, most commonly in the calf and psoas muscles.



24.67 Severity of haemophilia (ISTH criteria)

Severity	Factor VIII or IX level	Clinical presentation
Severe	< 0.01 U/mL	Spontaneous haemarthroses and muscle haematomas
Moderate	$0.01\text{--}0.05$ U/mL	Mild trauma or surgery causes bleeding
Mild	> 0.05 to 0.4 U/mL	Major injury or surgery results in excess bleeding

(ISTH = International Society on Thrombosis and Haemostasis)



Acute hemarthrosis of the knee is a common complication of hemophilia. It may be confused with acute infection unless the patient's coagulation disorder is known, because the knee is hot, red, swollen, and painful

Severe chronic arthritis in hemophilia. The knee is the most commonly affected joint. Both knees are severely deranged in this patient. Note that he is unable to stand with both feet flat on the floor.





Right retroperitoneal hematoma displacing the kidney anteriorly

Diagnosis

- ❖ Is confirmed by detection of significantly reduced factor VIII (hemophilia A) or IX (hemophilia B) activities in the plasma of:
 - Male babies born into families known to be affected by hemophilia or
 - Male children who present with excessive bruising or bleeding at the time of circumcision
 - When intramuscular injections of immunizing vaccinations are administered, or after trauma during the toddler years.
- ❖ prolongation of aPTT.

Management

In severe haemophilia A, bleeding episodes should be treated by raising the factor VIII level, usually by intravenous infusion of factor VIII concentrate. Factor VIII concentrates are freeze-dried and stable at 4°C and can therefore be stored in domestic refrigerators, allowing patients to treat themselves at home at the earliest indication of bleeding.

Resting of the bleeding site by either bed rest or a splint reduces continuing haemorrhage. Once bleeding has settled, the patient should be mobilised with physiotherapy.

The vasopressin receptor agonist DDAVP raises the vWF and factor VIII levels by 3–4-fold, which is useful in arresting bleeding in patients with mild or moderate haemophilia A.

FACTOR REPLACEMENT GUIDELINES FOR HEMOPHILIA A AND B

INJURY	FACTOR VIII INITIAL DOSE (U/kg)*	FACTOR IX INITIAL DOSE (U/kg)†
Dental prophylaxis	15-25	20-30
Hemarthrosis	15-25	30-50
Muscle hematoma	15-25	30-50
Trauma or surgery	50	100

*Dosing intervals should be based on a Factor VIII half-life of about 12 hours. Maintenance doses of one half the listed dose may be additionally provided at these intervals.

†Dosing intervals should be based on a Factor IX half-life of about 18 to 24 hours. Maintenance doses of one half the listed dose may be additionally provided at these intervals.



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Antihemophilic Factor
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Complications

Complications of hemophilia:

Osteoarthritis. A large psoas bleed may extend to compress the femoral nerve. Calf haematomas causing a compartment syndrome with subsequent contraction and shortening of the Achilles tendon.

Complications of coagulation factor therapy:

- Infection with HIV and hepatitis viruses HBV and HCV.
- Development of anti-factor VIII antibodies (20% of severe haemophiliacs). Such antibodies rapidly neutralise therapeutic infusions, making treatment relatively ineffective. Infusions of activated clotting factors, e.g. VIIa or factor VIII inhibitor bypass activity (FEIBA), may stop bleeding.

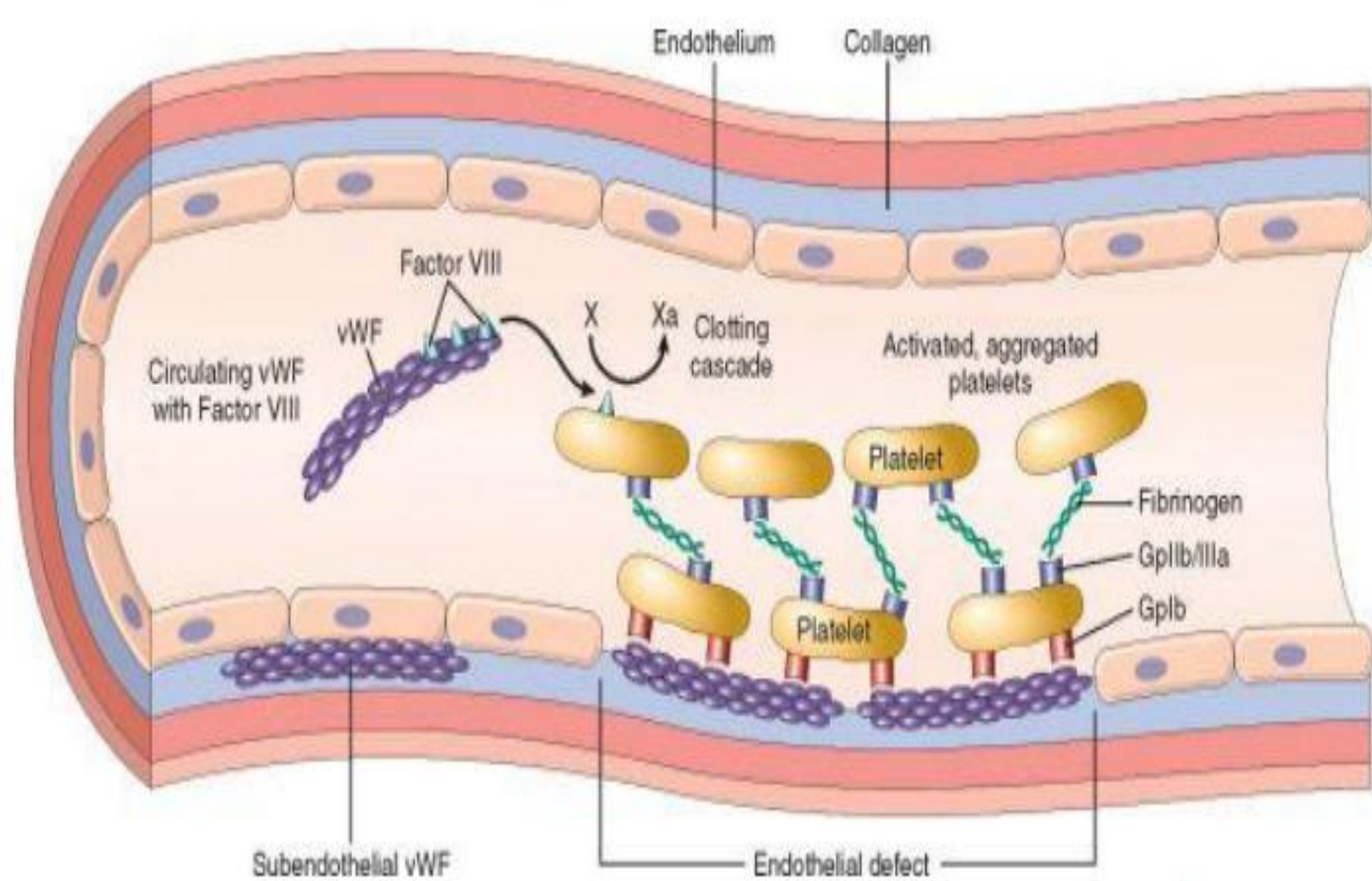
Haemophilia B (Christmas disease)

- It is X-linked recessive disease result in a reduction of the plasma factor IX level
- It is clinically indistinguishable from hemophilia A but is less common.
- The frequency of bleeding episodes is related to the severity of the deficiency of the plasma factor IX level.
- Treatment is with a factor IX concentrate, used in much the same way as factor VIII for hemophilia A. Although they do not commonly induce inhibitor antibodies (< 1% patients).

Acquired Hemophilias: Autoantibody inhibitors can occur spontaneously in individuals with previously normal hemostasis (nonhemophiliacs).

Von Willebrand disease:

- Von Willebrand disease is a common but usually mild bleeding disorder caused by a quantitative (types 1 and 3) or qualitative (type 2) deficiency of von Willebrand factor (vWF).
- The gene for vWF is located on chromosome 12 and the disease is usually inherited as an autosomal dominant, except in cases of type 2N and type 3, when it is recessive.
- vWF a protein synthesised by endothelial cells and megakaryocytes, which is involved in both platelet function and coagulation. It normally forms a multimeric structure which is essential for its interaction with subendothelial collagen and platelets.
- vWF acts as a carrier protein for factor VIII; deficiency of vWF lowers the plasma factor VIII level.



vWF tethers the platelet to exposed collagen

vWF serves as a carrier protein for factor VIII

Classification of von Willebrand disease

Type	Defect	Inheritance	Investigations
1	Partial quantitative	AD	Parallel decrease in vWF: Ag and VIII:c
2A	Qualitative	AD	Absent HWM of vWF Ratio of vWF activity to antigen < 0.7
2B	Qualitative	AD	Reduced HWM of vWF Enhanced platelet agglutination (RIPA)
2M	Qualitative	AD	Normal multimers of vWF Abnormal platelets Interactions
2N	Qualitative	AR	Defective binding of vWF to VIII Low VIII
3	Severe quantitative	AR or CH	Very low vWF activity and VIII:c Absent multimers

CH = compound heterozygote. HWM = high-weight multimers

Most patients with von Willebrand disease have a type 1 disorder, characterised by a quantitative decrease in a normal functional protein.

Clinical features

Patients present with haemorrhagic manifestations similar to those in individuals with reduced platelet function.

Superficial bruising, epistaxis, menorrhagia and gastrointestinal haemorrhage are common.

Within a single family, the disease has variable penetrance, so that some members may have quite severe and frequent bleeds, whereas others are relatively asymptomatic.

Investigations

Reduced vWF level, activity of vWF and factor VIII.

Prolonged bleeding time and aPTT time, but normal PT time.

In addition, analysis for mutations in the vWF gene is informative in most cases.

Treatment:

- Mild haemorrhage can be successfully treated by local means or with DDAVP and tranexamic acid.
- Serious or persistent bleeds, haemostasis can be achieved with selected factor VIII concentrates which contain considerable quantities of vWF in addition to factor VIII.
- Cryoprecipitate (contain fibrinogen, factor VIII and VWF) is used for prophylaxis or treatment of vWD-related bleeding complications.

Collecti



04 Z23920

CRYOPRECIPITATED AHF POOLED

No. Pooled Units 5
Volume 126 mL
50 mL of 0.9%
Sodium Chloride added.
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contraindications, cautions and methods of infusion.

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A pool of cryoprecipitate: it containing only fibrinogen, fibronectin, von Willebrand factor, factor VIII, and factor XIII. Individual units of cryoprecipitate typically contain 10 to 20 mL. Cryoprecipitate is stored in the frozen state at less than -18°C and must be thawed before issuing and administration. The shelf life while frozen is 1 year.

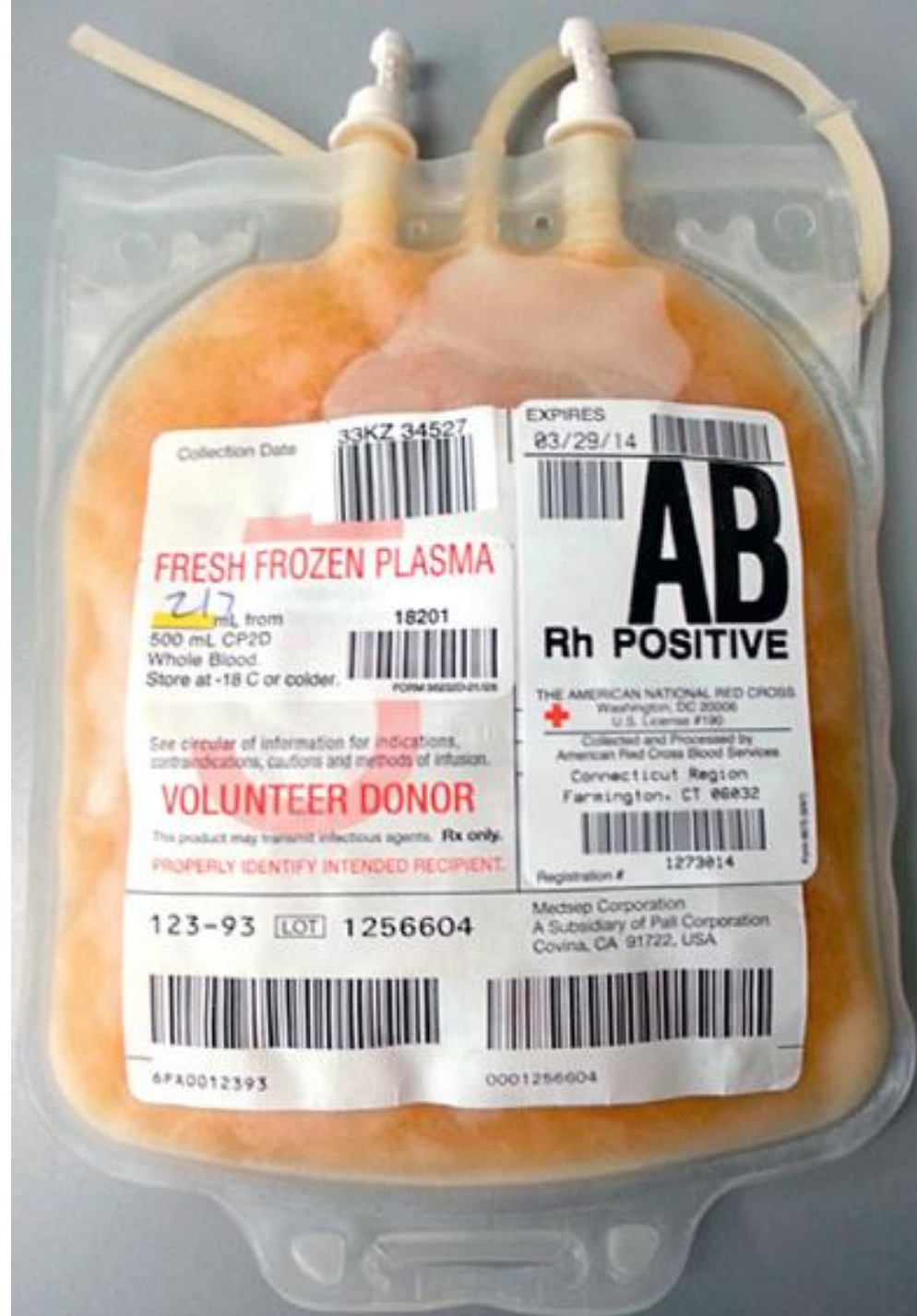
Acquired bleeding disorders

- DIC (previous lecture)
- Renal failure (previous lecture)
- **Liver failure:** There is reduced hepatic synthesis of factors V, VII, VIII, IX, X, XI, prothrombin and fibrinogen. Thrombocytopenia may occur secondary to hypersplenism in portal hypertension. In cholestatic jaundice, there is reduced vitamin K absorption, leading to deficiency of factors II, VII, IX and X.

The PT is a sensitive measure of liver function and becomes elevated in liver disorders.

Treatment with plasma products or platelet transfusion should be reserved for acute bleeds or to cover interventional procedures such as liver biopsy. Vitamin K deficiency can be readily corrected with parenteral administration of vitamin K.

Single unit of fresh-frozen plasma (FFP). contain a total volume of about 200 to 250 mL. FFP possesses all elements found in peripheral blood plasma, including coagulation factors, albumin, complement, and immunoglobulins, although they are primarily administered for coagulation factor defects. FFP is stored in the frozen state at less than -18°C and must be thawed before issuing and administration. The shelf life while frozen is 1 year.



Warfarin therapy bleeding:

warfarin inhibit the vitamin K-dependent carboxylation of factors II, VII, IX and X in the liver.

Major bleeding is the most common serious side effect of warfarin and occurs in 1–2% of patients each year. Fatal haemorrhage, most commonly intracranial, occurs in about 0.25% per annum.

Contraindications to anticoagulation are:

- Recent surgery, especially to eye or CNS
- Pre-existing haemorrhage state, e.g. liver disease, haemophilia, thrombocytopenia
- Pre-existing structural lesions, e.g. peptic ulcer
- Recent cerebral or gastrointestinal haemorrhage
- Uncontrolled hypertension
- Cognitive impairment
- Frequent falls

The international normalised ratio (INR) is validated only to assess the therapeutic effect of warfarin. INR is the ratio of the patient's PT to that of a normal control, raised to the power of the international sensitivity index of the thromboplastin used in the test (ISI, derived by comparison with an international reference standard material); (patient PT/mean control PT^{ISI}).

warfarin is administered in doses that produce a target INR of 2.0–3.0 and an increase in bleeding with INR values >4.5.

Treatment of warfarin over-anticoagulation and bleeding:

1- If the INR is above the therapeutic level in asymptomatic patients whose INR is between 3.5 and 4.5, warfarin should be withheld until the INR returns to the therapeutic range.

2- If the patient is not bleeding, it may be appropriate to give a small dose of vitamin K either orally or IV (1–2.5 mg), especially if the INR is greater than 8.

3- In the event of bleeding, withhold further warfarin.

- Minor bleeding can be treated with 1–2.5 mg of vitamin K IV.**
- Major haemorrhage should be treated as an emergency with vitamin K 5–10 mg slowly IV, combined with coagulation factor replacement. This should optimally be a prothrombin complex concentrate (30–50 U/kg) which contains factors II, VII, IX and X; if that is not available, fresh frozen plasma (15–30 mL/kg) should be given.**

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500 unit range for use with 20 mL vial
of Sterile Water for Injection, USP

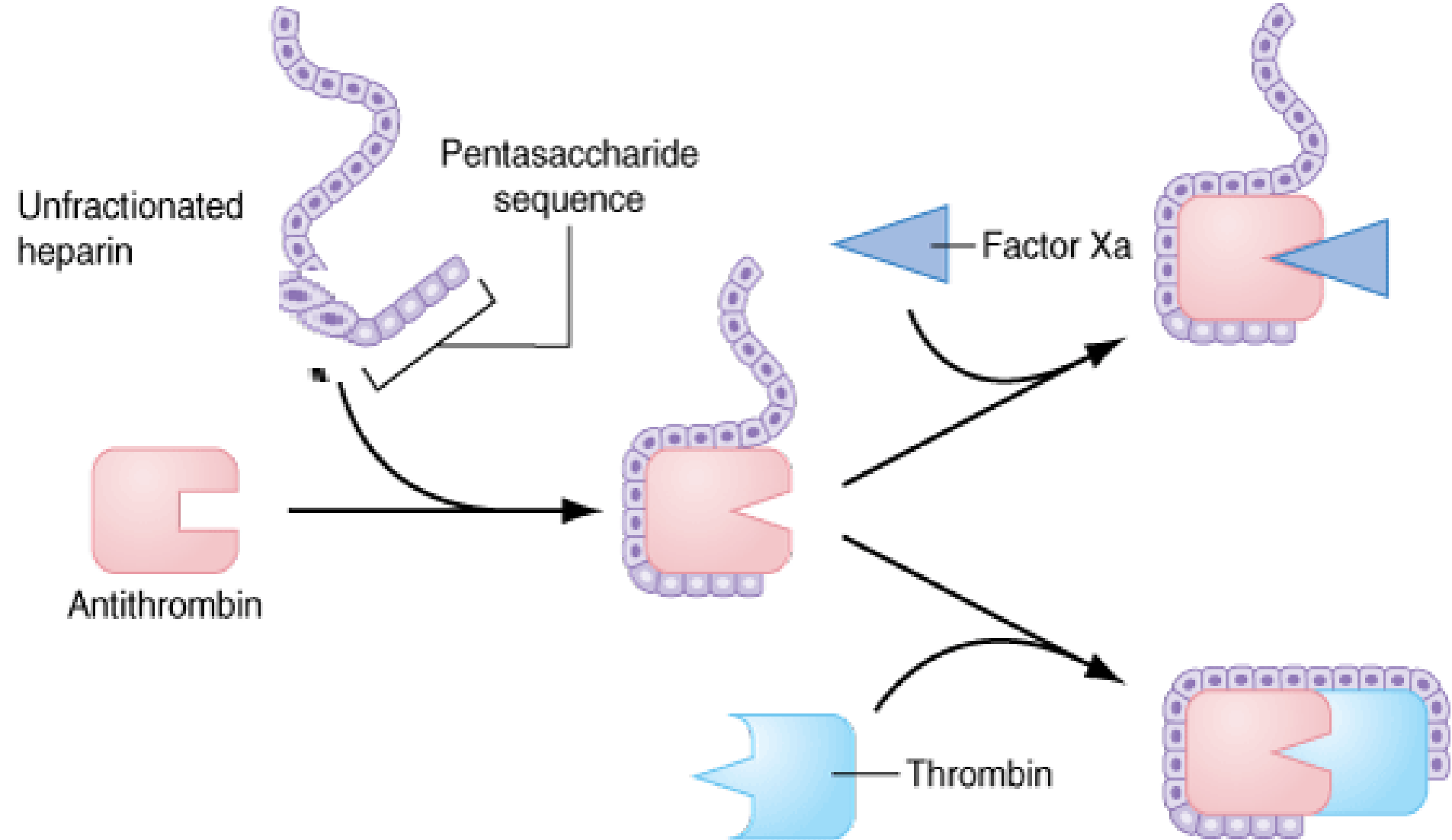
Heparin:

Heparin is a sulfated polysaccharide acts as an anticoagulant by activating antithrombin (previously known as antithrombin III) and accelerating the rate at which antithrombin inhibits clotting enzymes, particularly thrombin and factor Xa.

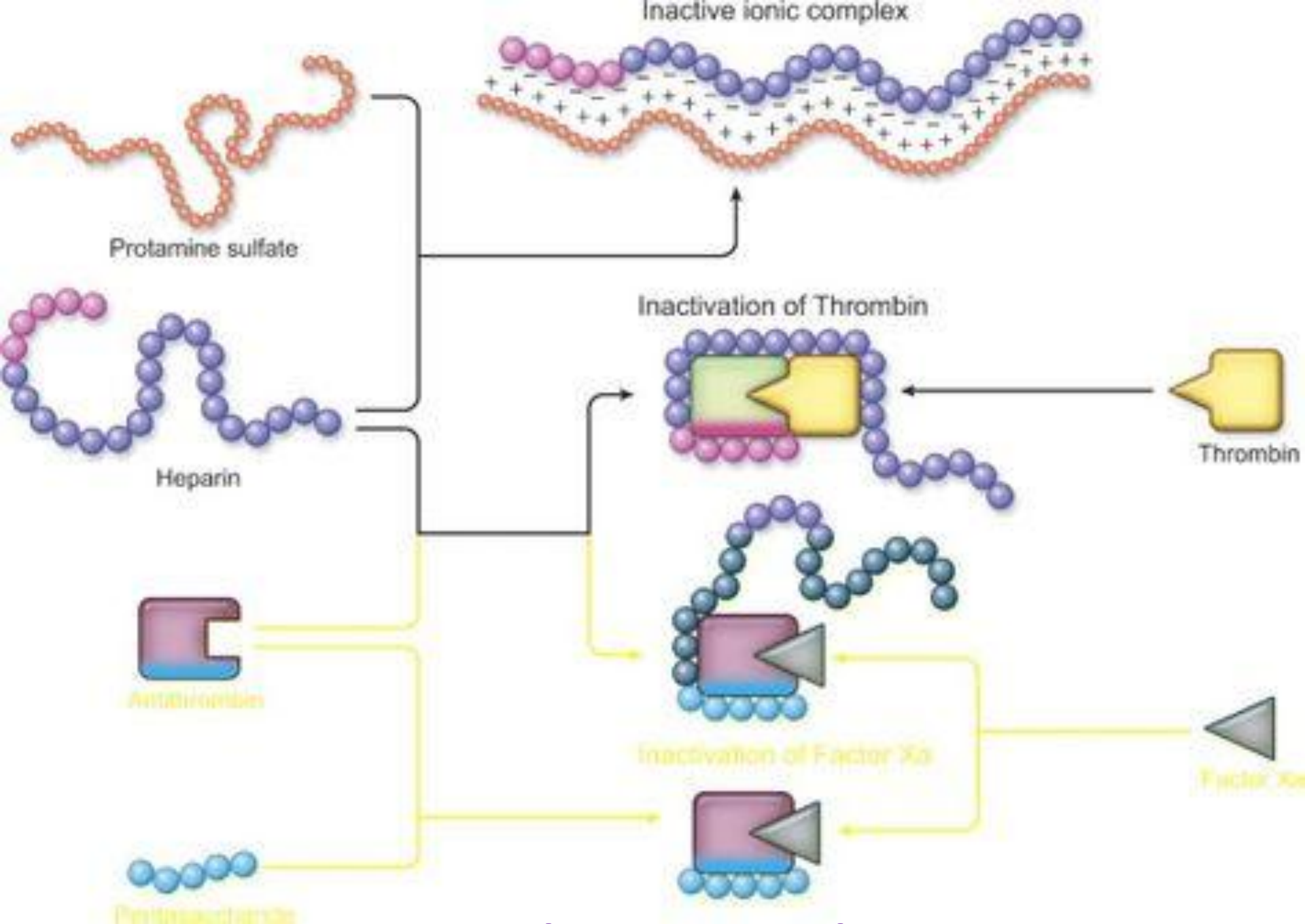
Heparin therapy can be monitored using the activated partial thromboplastin time (aPTT) or anti-factor Xa level.

Therapeutic heparin levels are achieved with a two- to threefold prolongation of the aPTT.

Heparin-treated patients with serious bleeding can be given protamine sulfate to neutralize the heparin and result in protamine-heparin complexes are then cleared. Typically, 1 mg of protamine sulfate neutralizes 100 units of heparin. Protamine sulfate is given by slow IV infusion.



Heparin binds to antithrombin via its pentasaccharide sequence. This induces a conformational change in the reactive center loop of antithrombin that accelerates its interaction with factor Xa. To potentiate thrombin inhibition, heparin must simultaneously bind to antithrombin and thrombin.



Protamine-heparin complexe

Thanks