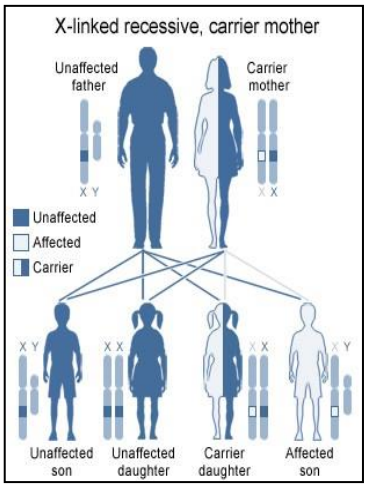
- **Hemostasis**: blood vessel injury → vasoconstriction → platelets adhesion → platelets aggregation → formation of platelet plug → formation of fibrin by coagulation cascade → fibrin will stabilize the primary platelet plug → leading to the formation of blood clot.
  Note: any defect or abnormality in one of these sequences (mainly: blood vessels, platelets or coagulation system) will result in bleeding disorders.
- **Coagulation system:**

| Extrinsic pathway | Intrinsic pathway |
|---|---|
| **Activated within**: seconds | **Activated within**: minutes |
| **Triggered by**: tissue trauma | **Triggered by**: blood trauma or contact with collagen |
| **Cascade**:<br>Tissue injury → Release of tissue factor (TF) → TF binding to factor VIIa → Formation of factor Xa → Factor Xa acting with factor V to form prothrombin activatior → Conversion of prothrombin to thrombin → Thrombin will convert fibrinogen to fibrin. | **Cascade**:<br>Blood trauma or contact with collagen → formation of factor XIIa → Formation of factor XIa → formation of factor IXa → factor IXa with factor VIII will activate factor X anf form factor Xa → Factor Xa acting with factor V to form prothrombin activatior → Conversion of prothrombin to thrombin → Thrombin will convert fibrinogen to fibrin. |

- **Common causes of coagulation disorders leading to bleeding:**
  - Von Willebrand Disease (VWD).
  - Hemophilia A or B
  - Disseminated intravascular coagulation (DIC).
  - Liver disease (because liver is the site of production of coagulation factors).
- **Features of bleeding disorders include:**
  - **Bleeding:**
    - ✓ From the skin and mucous membranes (nose, gums…etc) in case of disorders resulting from abnormalities in the vessels or platelets.
    - ✓ Into joints and soft tissues in case of disorders resulting from abnormalities in the coagulation system.
    - ✓ Menorrhagia (in females).
    - ✓ Easy bruising.
- **Hemophilia:**
  - **There are two main types of hemophilia (which are x-linked recessive):**
    - ✓ *Hemophilia A*: also know as classical hemophilia, characterized by deficiency in factor VIII & affects 1:5000 males.
    - ✓ *Hemophilia B:* also know as Christmas disease, characterized by deficiency in factor IX and affects 1:25,000 males.




  - **Clinical manifestations include:**

| Serious | Life threatening |
|---|---|
| Bleeding in joints (hemarthrosis) especially knee & elbow – bleeding in muscles & soft tissues – nose, gums & mouth bleeding – hematuria | Bleeding in CNS (rare) – GI bleeding – bleeding of neck & throat – severe trauma |

  - **Diagnosis:**
    - ✓ *PT*: normal
    - ✓ *APTT*: ↑
    - ✓ *Factor VIII or Factor IX levels*: ↓ (depending if hemophilia is type A or B).
    - ✓ *Family history*: positive (usually).
  - **Severity (related to factor VIII or factor IX levels):**
    - ✓ *Severe (<1%)*: spontaneous hemarthrosis.
    - ✓ *Moderate (1%-5%)*: gross bleeding following mild-moderate trauma.
    - ✓ *Mild (5%)*: severe hemorrhage only after severe trauma or surgery.

- **Treatment:**
  - ✓ Recombinant factor VIII or factor IX. The problem is that with prolonged-therapy with these recombinant factors, the patient is going to develop antibodies against them. This requires bypassing these factors by FEIBA or factor VIIa.

- **Von Willebrand Disease (VWD):**

- It is an autosomal dominant (AD) disease characterized by mutations in VWF which is found on chromosome 12. VWF is produced in endothelial cells & megakaryocytes and stored in Weibel-palade bodies as Ultra Large Von Willebrand Factor (ULVWF).
- ULVWF is cleaved in the plasma by ADAMTS13 metalloprotease.
- **VWF functions:**
  - ✓ Aid in the adhesion of platelets.
  - ✓ Carrying factor VIII & prolonging its half life (t1/2).
- **Clinical features include:**
  - ✓ Bleeding from skin (easy bruising) and mucous membranes (epistaxis).
  - ✓ Prolonged bleeding after minor trauma.
  - ✓ Menorrhagia in women (with varying severity).
- **Types of Von Willebrand Disease:**

| | Type 1 | Type 2 | Type 3 | Platelet type |
|---|---|---|---|---|
| Inheritance | AD | AD | AR | AD |
| Frequency | 70-80 | 10-12 | 1-3 | 0-3 |
| Bleeding time | N | ↑ed | ↑ed | ↑ed |
| Platelets | N | N | N | ↓ed |
| FVIII | ↓ed | N | absent | N |
| VWF:Ag | ↓ed | ↓ed | absent | N/↓ed |
| VWF activity | ↓ed | ↓ed | absent | N/↓ed |

- **Lab investigations:**
  - ✓ *PT*: normal
  - ✓ *APTT*: ↑
  - ✓ *Factor VIII level*: ↓ (but it is normal in type 2)
  - ✓ *Ristocetin*: ↓
  - ✓ *VWF antigen*: ↓ (in type 1 and 3).
- **Treatment:**
  - ✓ Desmopressin (DDAVP).