HEMOSTASIS, BLEEDING & CLOTTING DISORDER

In the absence of blood vessel damage :

- platelets are repelled
  - from each other &
  - from endothelium of blood vessel.

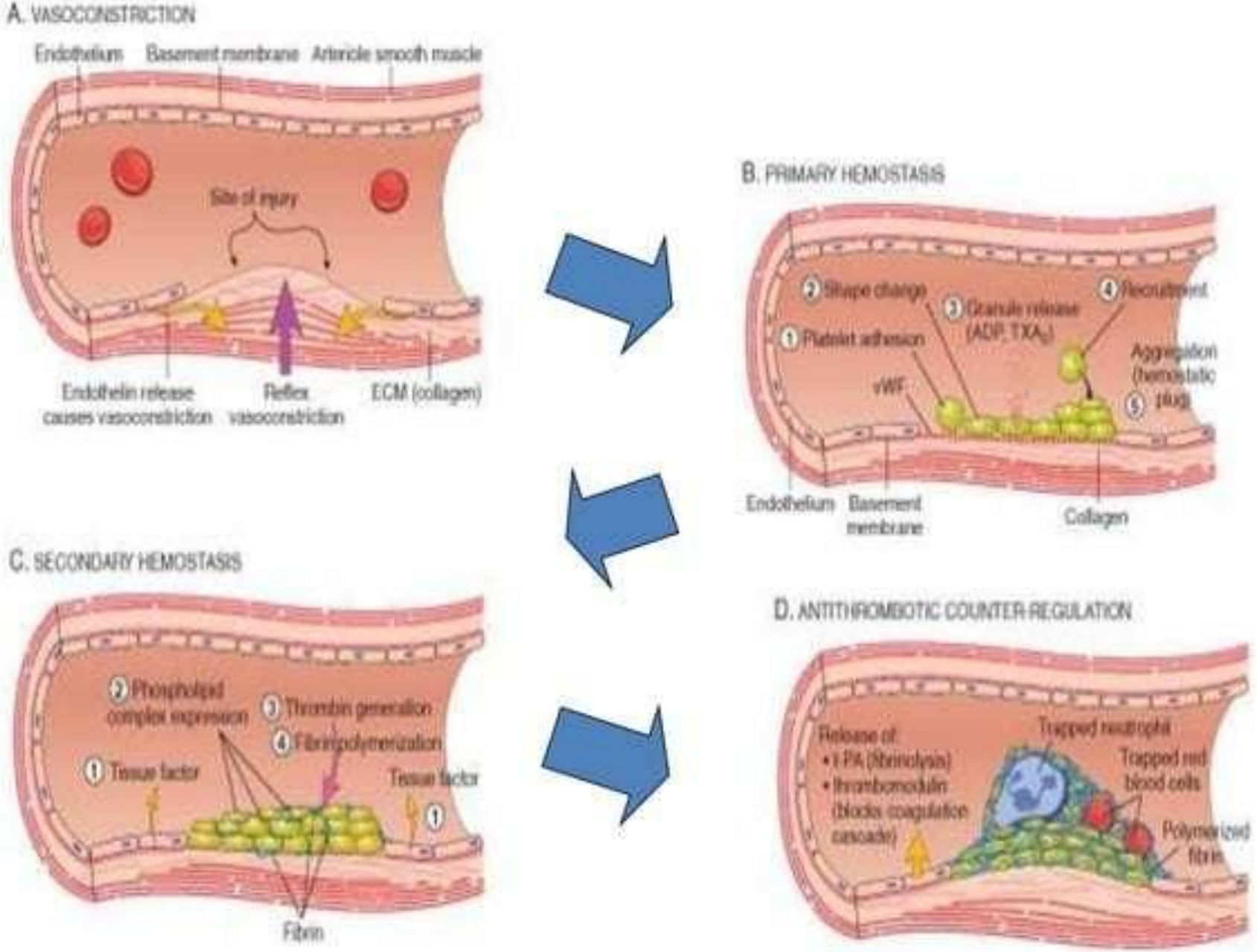
- endothelial cell secretes
  - prostacyclin &
  - nitric oxide (NO)

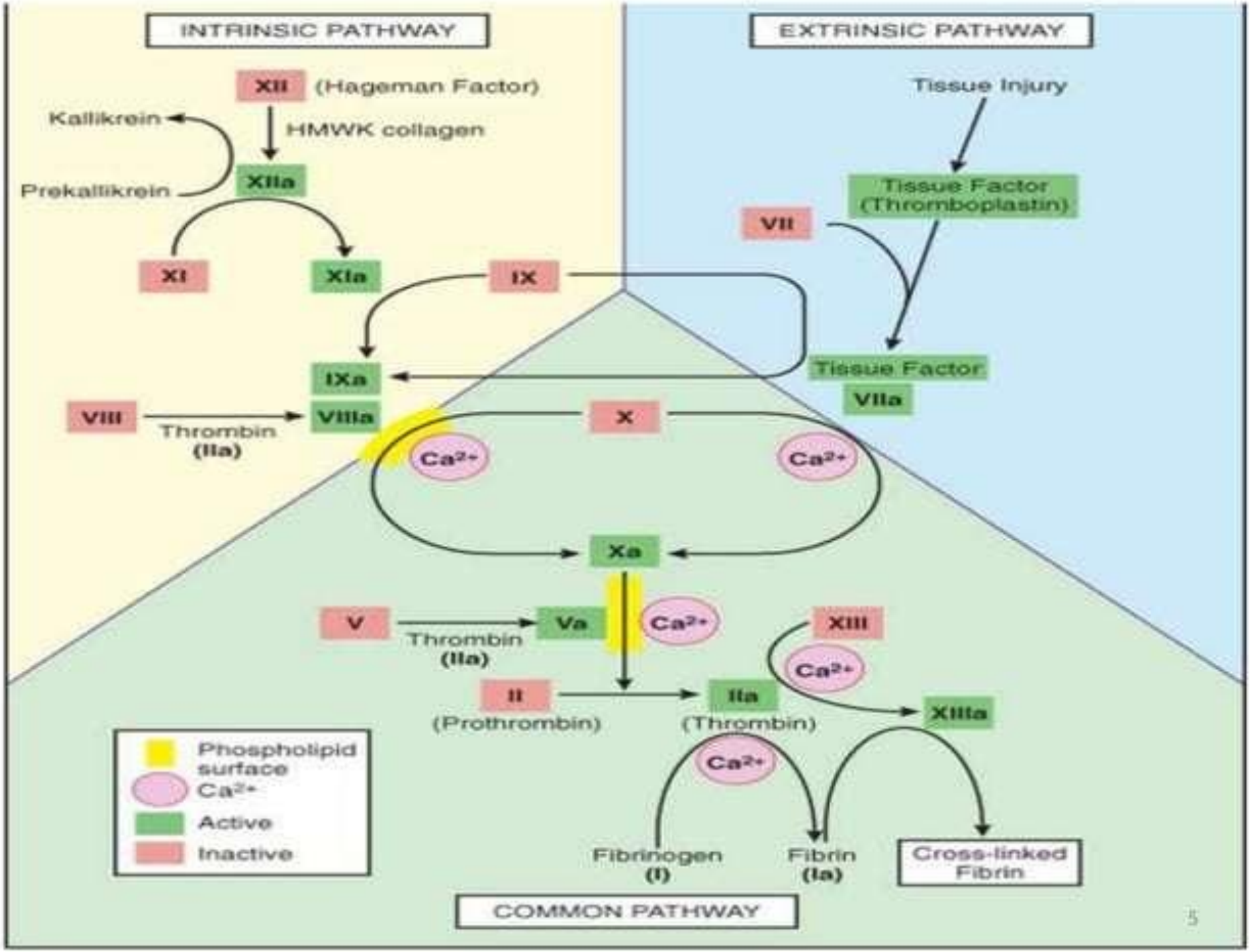
  act as vasodilator & inhibit platelet aggregation.

- plasma membrane of endothelial cell contain enzyme (CD39) - breakdown ADP to AMP + Pi.

Normal Hemostasis

- Def : consequence of tightly regulated processes that maintain blood in a fluid, clot-free state in normal vessels while introducing the rapid formation of a localized hemostatic plug at the site of vascular injury.
- Mechanism
  - ❑ vasocontriction
  - ❑ formation of platelet plug
  - ❑ coagulation cascade
  - ❑ fibrinolysis


A. VASOCONSTRICTION
Endothelium
Basement membrane
Arteriole smooth muscle
Site of injury
Endothelin release causes vasoconstriction
Reflex vasoconstriction
ECM (collagen)
B. PRIMARY HEMOSTASIS
2 Shape change
3 Granule release (ADP, TXA2)
4 Recruitment
1 Platelet adhesion
vWF
Aggregation (hemostatic plug)
Endothelium
Basement membrane
Collagen
C. SECONDARY HEMOSTASIS
2 Phospholipid complex expression
3 Thrombin generation
4 Fibrinopolymerization
1 Tissue factor
Tissue factor
1
Fibrin
D. ANTITHROMBOTIC COUNTER-REGULATION
Release of:
• t-PA (fibrinolysis)
• thrombomodulin (blocks coagulation cascade)
Trapped neutrophil
Trapped red blood cells
Polymerized fibrin


INTRINSIC PATHWAY
EXTRINSIC PATHWAY
XII
(Hageman Factor)
HMWK collagen
Kallikrein
Prekallikrein
XIIa
XI
XIa
IX
Tissue Injury
Tissue Factor
(Thromboplastin)
VII
IXa
Tissue Factor
VIIa
VIII
Thrombin
(IIa)
VIIIa
X
Ca2+
Ca2+
Xa
V
Thrombin
(IIa)
Va
Ca2+
XIII
Ca2+
II
(Prothrombin)
IIa
(Thrombin)
XIIIa
Ca2+
Phospholipid surface
Ca2+
Active
Inactive
Fibrinogen
(I)
Fibrin
(Ia)
Cross-linked Fibrin
COMMON PATHWAY

Hemorrhagic Disorder

- It is a general term for a wide range of medical problems that lead to poor blood clotting & continuous bleeding.
  - characterized clinically by abnormal bleeding, which can either be spontaneous or become evident after some inciting event.

- can result from :
  - ➢ Defects in the blood vessel [Vascular abnormality]
  - ➢ abnormalities in the blood itself
    - ❖ Defect in blood clotting factor
      - ✓ Defficiency of coagulation factor
      - ✓ Inhibitors of coagulation factor
      - ✓ Defect in platelet function
    - ❖ Defect in Platelet
      - ❖ Qualititative (Thrombocytopathia)
      - ❖ Quantitative (Thrombocytopenia)

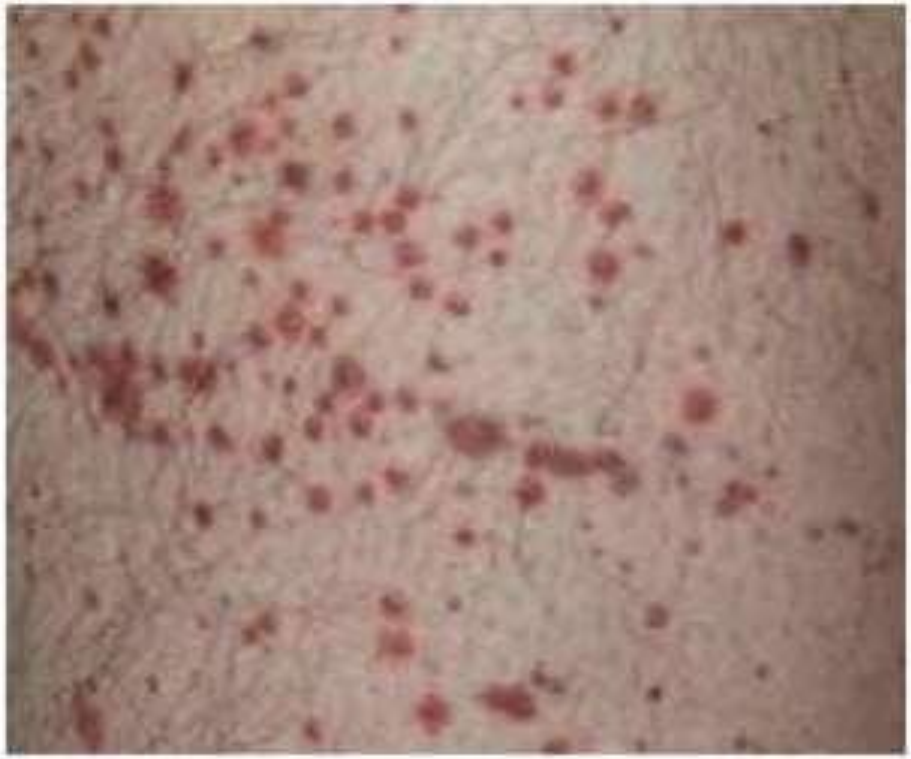
- Defects in blood vessel [Vascular abnormality]
  - It may be:
    - Inherited
    - Acquired
- **Inherited**
  - Rare disorder
  - Autosomal dominant trait
  - Most common inTelangiectasia
    - In this, dilation of small vessel occurs.
    - Complication may lead to Fe- defficiency anemia.

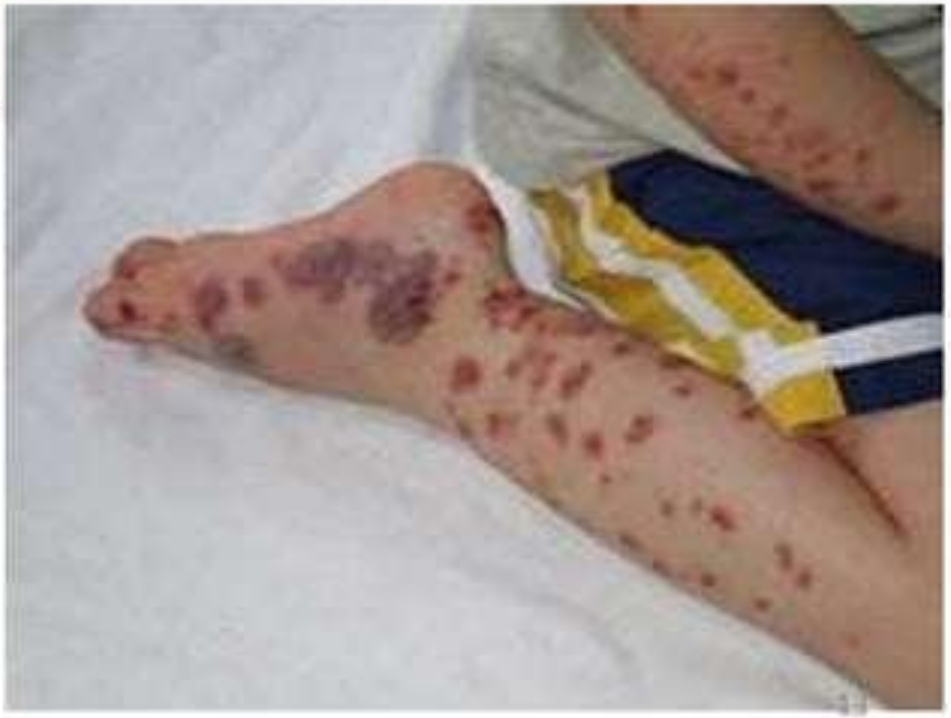
- Defects in blood vessel [Vascular abnormality]
  - It may be:
    - Inherited
    - Acquired
- **Acquired**
  - More common
  - Usually related to some other disease.
    - Simple easy bruising
    - Senile purpura
    - Steroid purpura
    - Scurvy
    - Henoch scholein syndrome

- **Simple easy bruising**
  - It is benign disorder which occur in healthy women of child bearing age.
- **Senile purpura**
  - It occurs due to atrophy of supporting tissue.
- **Steroid purpura**
  - It is associated with cushing's syndrome.
  - It occurs due to abnormality of supporting tissue due to long term use of steroid.

- **Scurvy**
  - It occurs due to vit. C deficiency.
  - Vit. C is req. for collagen synthesis.
    - Hydroxylation of proline and lysine require vitamin C as a cofactor of the enzymes.
      - Hydroxyproline: involved in H-bond formation & thus stabilize triple helix,
      - Hydroxylysine: sites of attachment of disaccharide moieties (galactose-glucose).
  - Lack of collagen leads to weak blood vessel & thus bleeding tendency.

- **Henoch scholein syndrome**
  - Type of hypersensitivity reaction
  - Purpura, arthritis & abdominal pain are known as the "classic triad" of Henoch–Schönlein purpura
  - HSPis a small-vessel vasculitis in which complexes of IgA & complement component 3 (C3) are deposited on arterioles, capillaries, and venules.
    - Leading to ↑ed vascular permeability & thus easy bleeding
  - HSP involves the skin, connective tissues, scrotum, joints, GIT & kidneys.





- **Defects in coagulation factor**
  - **Inherited**
    - Hemophilia A
    - Hemophilia B
    - Hemophilia C
    - von-Willebrand disease
  - **Acquired**
    - Vit. K deficiency
    - Heparin therapy
    - DIC
    - Lupus type anticoagulant

Hemophilia A

- also called
  - –Factor VIII (FVIII) deficiency
  - –classic hemophilia
- **Hemophilia A** is a hereditary (genetic) bleeding disorder caused by missing or defective factor VIII, which causes ↑ed bleeding
- Usually affects males & homozygous females.
  - – 70% of cases: inherited as an X-linked recessive trait
  - – 30% of cases: arise from spontaneous mutations.
- [Without enough factor VIII, blood cannot clot properly to stop bleeding.]

- Factor VIII has two active components:-
  - a large component [mol. Wt. in millions]
  - &a smaller component [mol. Wt. of about 230,000]
- The smaller component is most imp. in intrinsic pathway for clotting, & its deficiency causes classic hemophilia.
- In 5-10% cases: patients make a dysfunctional version of the factor VIII protein (qualitative deficiency)
- In 90-95% cases: patients produce factor VIII in insufficient amounts (quantitative deficiency).

Genetics of Hemophilia A

- Hemophilia is inherited in an X-linked recessive manner.
- Hemophilic gene is carried on X chromosome.
- Females inherit XX chromosomes & males XY.
  - That means if a son inherits an X chromosome carrying hemophilia from his mother, he will have hemophilia.
  - It also means that fathers cannot pass hemophilia on to their sons.
- Even if Daughters inherit hemophilic gene from their mother, most likely they inherit a healthy X chromosome from father & not have hemophilia.

- A daughter who inherits an X chromosome that contains the gene for hemophilia is called a carrier.
  - She can pass the gene on to her children.
  - Hemophilia can occur in daughters, but is rare.
- For a female carrier, there are four possible outcomes for each pregnancy:
  1. A girl who is not a carrier
  2. A girl who is a carrier
  3. A boy without hemophilia
  4. A boy with hemophilia

Types on the basis of severity

- There are numerous diff. mutations which cause hemophilia A.
- Due to differences in changes to the gene involved (& the subsequent resulting protein), patients with hemophilia often have some level of active clotting factor.
- Individuals according to the level of active factor VIII are classified as having severe, moderate, mild hemophilia.

	factor levels	Represents approximately
Severe	**(<0.01U/mL)**	**60% of cases**
Moderate	**(0.02-0.05 U/mL)**	**15% of cases**
Mild	**(>0.05U/mL)**	**25% of cases**

Symptoms

- People with hemophilia A often, bleed longer than other people.
- In general, symptoms are internal or external bleeding episodes, which are called "bleeds".
  - Bleeds can occur:
    - internally, into joints and muscles
    - externally, from minor cuts, dental procedures or trauma.

- Symptoms may include:
  - Bleeding into joints with associated pain and swelling
  - Blood in the urine or stool
  - Bruising
  - GIT & urinary tract hemorrhage
  - Nose bleeds
  - Prolonged bleeding from
    - Cuts
    - tooth extraction
    - and surgery
  - Spontaneous bleeding

- **Mild hemophilia A**
  - People with mild hemophilia A generally experience bleeding only after serious injury, trauma or surgery.
  - In many cases, mild hemophilia is not diagnosed until an injury, surgery or tooth extraction results in prolonged bleeding.
  - The first episode may not occur until adulthood.
  - Women with mild hemophilia often experience:
    - menorrhagia,
    - heavy menstrual periods
    - & can hemorrhage after child birth.

- **Moderate hemophilia A**
  - People with moderate hemophilia A tend to have bleeding episodes after injuries.
  - Bleeds that occur without obvious cause are called spontaneous bleeding episodes.
- **Severe hemophilia A**
  - People with severe hemophilia A experience bleeding following an injury and may have frequent spontaneous bleeding episodes, often into their joints and muscles.

Tests to diagnose hemophilia A include:

- **Factor VIII : Markedly ↓ed**
- **APTT : Increased**
- **PTT : Increased**
- **Bleeding time : Normal**
- **Platelet count : Normal**
- **Fibrinogen level : Normal**
- **Prothrombin time : Normal**
- **Thrombin time : Normal**

- **Hemophilia B [Christmas disease]**
  - Also inherited (x-linked) disorder.
  - 5 times less frequent than hemophilia A.
  - Genetics is similar to hemophilia A.
  - Lab diagnosis
    - » Similar to hemophilia A except
      - Factor IX is deficient

- **Hemophilia C [Rosenthial syndrome]**
  - Rarely found
  - All clinical features is similar to hemophilia A & B.
  - Lab diagnosis
    - » Similar to hemophilia A except
      - Factor XI is deficient

- **Von-willibrand disease**
  - vWD is named after Erik Adolf von Willebrand, a Finnish pediatrician who 1st described it in 1926.
  - Most common hereditary coagulation abnormality described in humans, although it can also be acquired as a result of other medical conditions.
  - It arises from a qualitative or quantitative deficiency of von Willebrand factor (vWF), a multimeric protein that is required for platelet adhesion.
  - factor VIII is bound to vWF which protects the factor VIII from rapid breakdown within the blood.
  - Deficiency of vWF can therefore lead to a reduction in factor VIII levels

- **Von-willibrand disease**
  - There are three forms of vWD:
    - inherited,
    - acquired,
    - & pseudo or platelet type.
  - There are 3 types of hereditary vWD:
    - vWD Type I,
    - vWD Type II,
    - & vWD III.
      - Within the three inherited types of vWD there are various subtypes.

- **Von-willibrand disease**
  - Platelet type vWD is also an inherited condition.
  - vWD Type I is most common type of the disorder & those that have it are typically asymptomatic or may experience mild symptoms such as nose bleeds although there may be severe symptoms in some cases.
  - There are various factors that affect the presentation and severity of symptoms of vWD such as blood type.

- **Type 1 vWD**
  - Type 1 vWD (60-80%) is a quantitative defect which is heterozygous for the defective gene.
  - von Willebrand factor production is decreased. [10-45 IU]
  - Many patients are asymptomatic or may have mild symptoms and not have clearly impaired clotting which might suggest a bleeding disorder.

- **Type 2**
  - Type 2 vWD (20-30%) is a qualitative defect
  - Bleeding tendency can vary between individuals.
  - There are normal levels of vWF, but the multimers are structurally abnormal, or subgroups of large or small multimers are absent.
  - Four subtypes exist: 2A, 2B, 2M and 2N.

- **Type 2A**
  - Ability of vWF to bind to the glycoprotein1 (GP1) receptor on the platelet membrane is diminished, resulting in:
    - ↓ed platelet adhesiveness & aggregation
    - abnormally low ristocetin cofactor activity.
  - The ability of the defective vWF to coalesce & form large vWF multimers is also impaired, resulting in ↓ed quantity of large vWF multimers.

- **Type 2B**
  - This is a "gain of function" defect.
  - The ability of the qualitatively defective vWF to bind to glycoprotein1 (GP1) receptor on platelet membrane is abnormally enhanced, leading to its spontaneous binding to platelets and subsequent rapid clearance of the bound platelets and of the large vWF multimers.
  - Thrombocytopenia may occur.
  - Large vWF multimers are reduced or absent from the circulation.

- **Type 2M**
  - It is a qualitative defect of vWF characterized by its ↓ed ability to bind to glycoprotein1 (GP1) receptor on platelet membrane & normal capability at multimerization.
  - The vWF antigen levels are normal.
  - The ristocetin cofactor activity is ↓ed.
  - & high molecular weight large vWF multimers are +nt in circulation.

- **Type 2N (Normandy)**
  - This is a deficiency of the binding of vWF to coagulation factor VIII.
  - Quantity of vWF is normal.
  - Ristocetin cofactor is normal
  - Factor VIII markedly decrease equivalent to levels seen in hemophilia A.
  - This has led to some vWD type 2N patients being misdiagnosed as having hemophilia A.

- **Type 3**
  - It is the most severe form of vWD (homozygous for defective gene)
  - Characterized by complete -nce of production of vWF. [vWF is undetectable]
  - Since vWF protects coagulation Factor VIII from proteolytic degradation, total -nce of vWF leads to extremely low Factor VIII level.
  - Inheritance pattern: Autosomal recessive.

- **Platelet-type** (also known as pseudo-vWD)
  - Autosomal dominant
  - The vWF is qualitatively normal and no mutational alteration of the von Willebrand gene.
  - The defect lies in the qualitatively altered glycoprotein1 (GP1) receptor on platelet membrane.
  - Large platelet aggregates & high molecular weight vWF multimers are removed from circulation resulting in thrombocytopenia & diminished or -nt large vWF multimers.
  - Low ristocetin cofactor activity
  - Loss of large vWF multimers

- **Acquired von Willebrand disease**
  - Acquired vWD can occur in patients with autoantibodies.
  - In this case the function of vWF is not inhibited but the vWF-antibody complex is rapidly cleared from the circulation.
  - A form of vWD occurs in patients with aortic valve stenosis, leading to GIT bleeding (Heyde's syndrome).
  - Thrombocythemia is another cause of acquired vWD, due to sequestration of vWF via adhesion of vast numbers of platelets.
  - Acquired vWD has also been observed in the following disorders: Wilm's tumour, hypothyroidism and mesenchymal dysplasias.

Decreased Prothrombin, Factor VII, Factor IX, & Factor X Caused by Vitamin K Deficiency

- In -nce of vit. K, subsequent insufficiency of these coagulation factors in blood, lead to serious bleeding tendencies.
- Vit. K is continually synthesized by intestinal flora, thus vit. K def. seldom occurs in the normal person as a dietary def. of vit. K (except in neonates before they establish their intestinal bacterial flora).

Decreased Prothrombin, Factor VII, Factor IX, & Factor X Caused by Vitamin K Deficiency

- However, in GI-disease, vit. K def. often occurs as a result of poor absorption of fats from GIT.
  - Vit. K (fat-soluble) is absorbed along with fats.
- One of the most prevalent causes of vit. K def. is failure of liver to secrete bile into the GIT (as a result of obstruction of the bile ducts or liver disease).
  - Lack of bile prevents adequate fat digestion & absorption,& thus depresses vit. K absorption as well.

Decreased Prothrombin, Factor VII, Factor IX, & Factor X Caused by Vitamin K Deficiency

- Thus, liver disease causes ↓ed production of prothrombin & some other clotting factors because of:-
  - poor vitamin K absorption
  - & diseased liver cells.
- Thus, vit. K is injected into all surgical patients with:-
  - liver disease
  - obstructed bile ducts.

  } before performing the surgical procedure
- Ordinarily, if vitamin K is given to a deficient patient 4 to 8 hrs before the operation and the liver parenchymal cells are at least one-half normal in function, sufficient clotting factors will be produced to prevent excessive bleeding during the operation.

Decreased Prothrombin, Factor VII, Factor IX, & Factor X Caused by Vitamin K Deficiency

- Increased PT & PTT
- Normal platelet count & fibrinogen

- **Liver disease**
  - The coagulopathy associated with liver disease is complex & multifactorial.
  - Liver synthesizes most of the coagulation factors.
  - Thus in liver disease, decreased synthesis of coagulation factor occurs.
  - **Lab diagnosis**
    - Low platelet count
    - Prolonged PT & APTT
    - Normal thrombin time

- **Diffused intravascular coagulation**
  - Most common thrombohemorrhagic disorder.
  - In this intravascular clotting leads to utilization of coagulation factor & platelet, thereby leading to hemostatic defect

❖ Defect in Platelet

❖ Qualititative (Thrombocytopathia)

1. Failure of platelet to adhere
2. Failure of platelet to produce ADP
3. Failure of platelet to respond to ADP
4. Failure of platelet to produce thromboxane A_2
5. Failure of platelet to bind to coagulation factor

❖ Quantitative (Thrombocytopenia)

1. Decreased platelet production
2. Increased platelet destruction
3. Abnormal platelet distribution
4. Dilution loss
5. Idiopapathic causes

- **Failure of platelet to adhere**
  - Due to spleenic effect
    - Eg: Bernard Soulier syndrome
- **Failure of platelet to produce ADP**
  - Two conditions
    - Inability of platelet to produce ATP
    - Inability of platelet to release ADP
  - These arises due to inability of platelet to produce prostaglandins.

- **Failure of platelet to respond to ADP**
  - Inherited disorder
  - Platelet fails to respond to ATP & thus to aggregation of platelet.
  - It occurs due to lack of specific glycoprotein in platelet
- **Failure of platelet to bind to coagulation factor**
  - It may occur if:
    - Platelet fail to aggregate
    - Platelet fail to shape
    - Shortage of coagulation factor

- **Decreased platelet production**
  - It may be due to:
    - Depression of megakaryocytes
    - Bone marrow failure
      - Most common
      - May be due to:
        - Radiation
        - Iatrogenic chemical
        - Toxic chemical
        - Competition for nutrients between normal & cancer cells

- **Increased platelet destruction**
  - Severe & premature destruction of platelet leads to thrombocytopenia
  - But mild destruction don't lead to thrombocytopenia (due to compensation by megakaryocyte mass)
  - It occurs due to:
    - Autoimmune activity
    - Mechanical destruction
    - Septicemia
    - Idiopathic

- **Abnormal platelet distribution**
  - 1/3rd of total platelet is present in spleen.
  - In spleenomegaly, this pool in spleen is ↑ed.
  - If BM is unable to compensate for bone marrow's pool size, leads to thrombocytopenia.
- **Dilutional loss**
  - Transfused blood often contain platelets.
  - Any persons have undergone multiple blood transfusion have less no. of platelet due to dilution of blood.

Condition	Prothrombin time	Partial thromboplastin time	Bleeding time	Platelet count
Vitamin K deficiency or warfarin	Prolonged	Normal or mildly prolonged	Unaffected	Unaffected
Disseminated intravascular coagulation	Prolonged	Prolonged	Prolonged	Decreased
Von Willebrand disease	Unaffected	Prolonged or unaffected	Prolonged	Unaffected
Hemophilia	Unaffected	Prolonged	Unaffected	Unaffected
Aspirin	Unaffected	Unaffected	Prolonged	Unaffected
Thrombocytopenia	Unaffected	Unaffected	Prolonged	Decreased
Liver failure, early	Prolonged	Unaffected	Unaffected	Unaffected
Liver failure, end-stage	Prolonged	Prolonged	Prolonged	Decreased
Uremia	Unaffected	Unaffected	Prolonged	Unaffected
Congenital afibrinogenemia	Prolonged	Prolonged	Prolonged	Unaffected
Factor V deficiency	Prolonged	Prolonged	Unaffected	Unaffected
Factor X deficiency as seen in amyloid purpura	Prolonged	Prolonged	Unaffected	Unaffected
Glanzmann's thrombasthenia	Unaffected	Unaffected	Prolonged	Unaffected
Bernard-Soulier syndrome	Unaffected	Unaffected	Prolonged	Decreased or unaffected
Factor XII deficiency	Unaffected	Prolonged	Unaffected	Unaffected
C1INH deficiency	Unaffected	Shortened	Unaffected	Unaffected