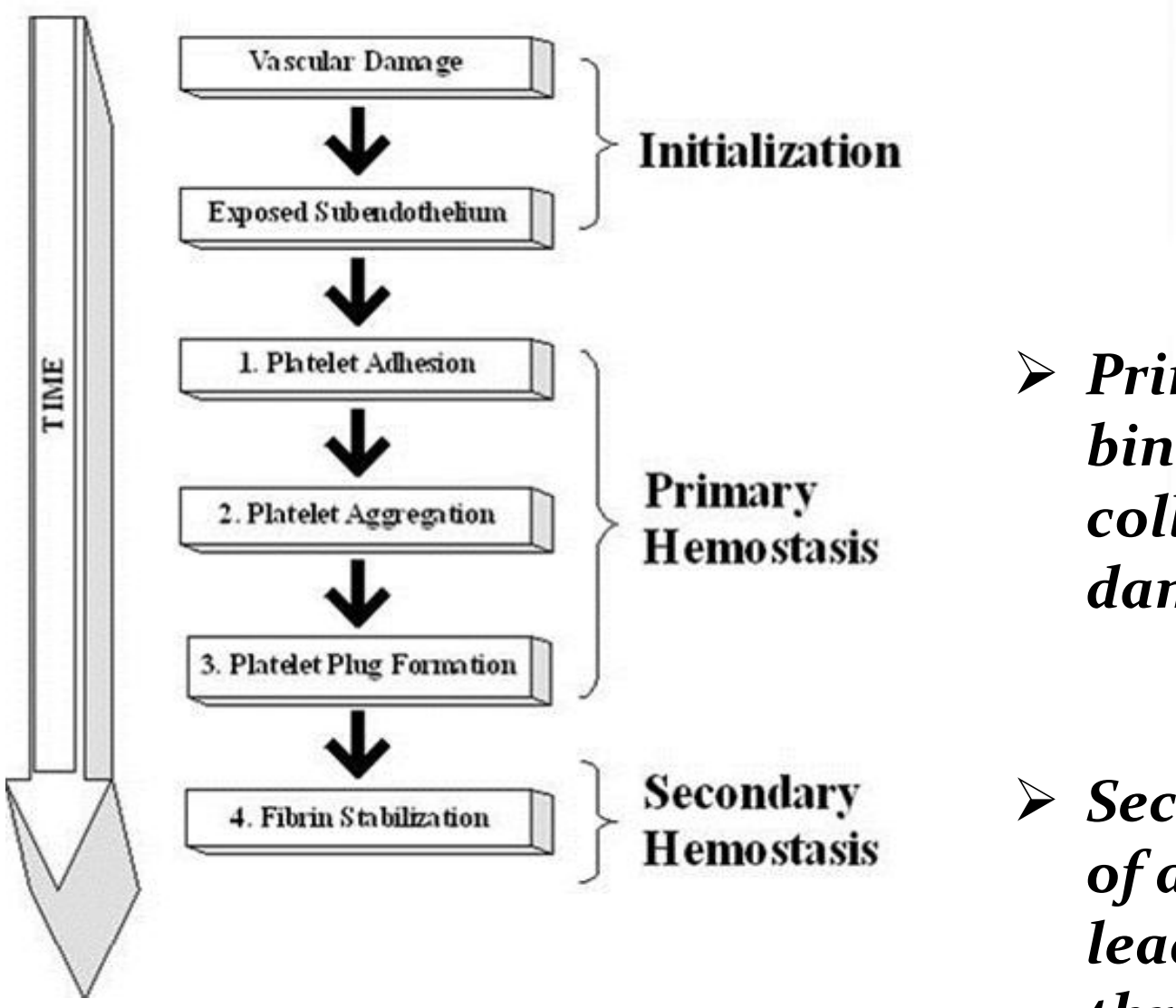
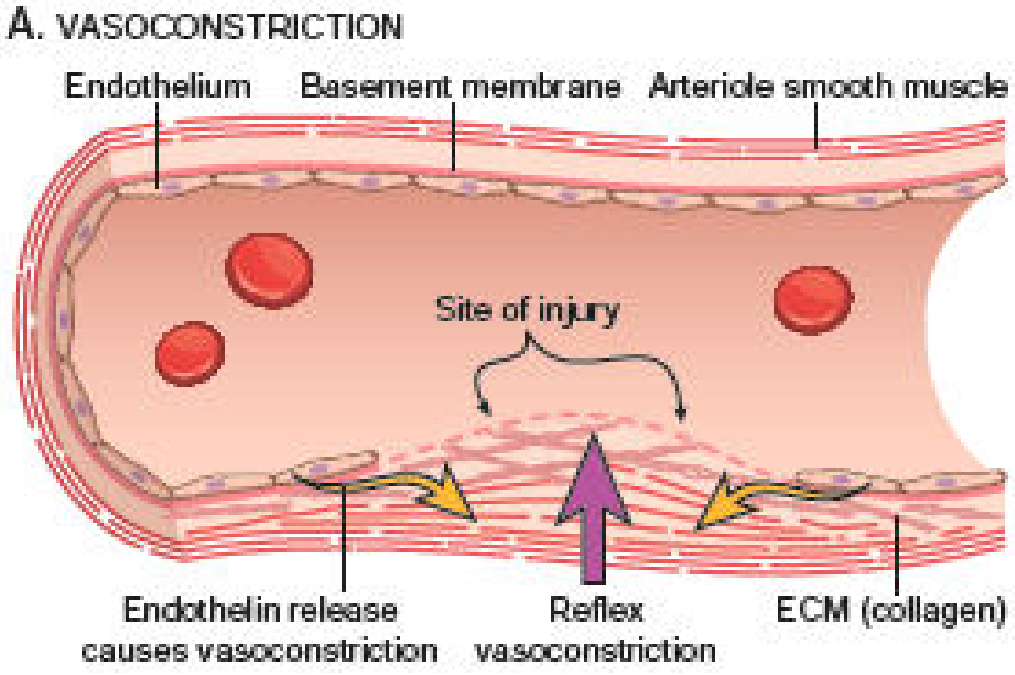
Approach to Bleeding Disorders

Overview of Hemostatic Mechanisms

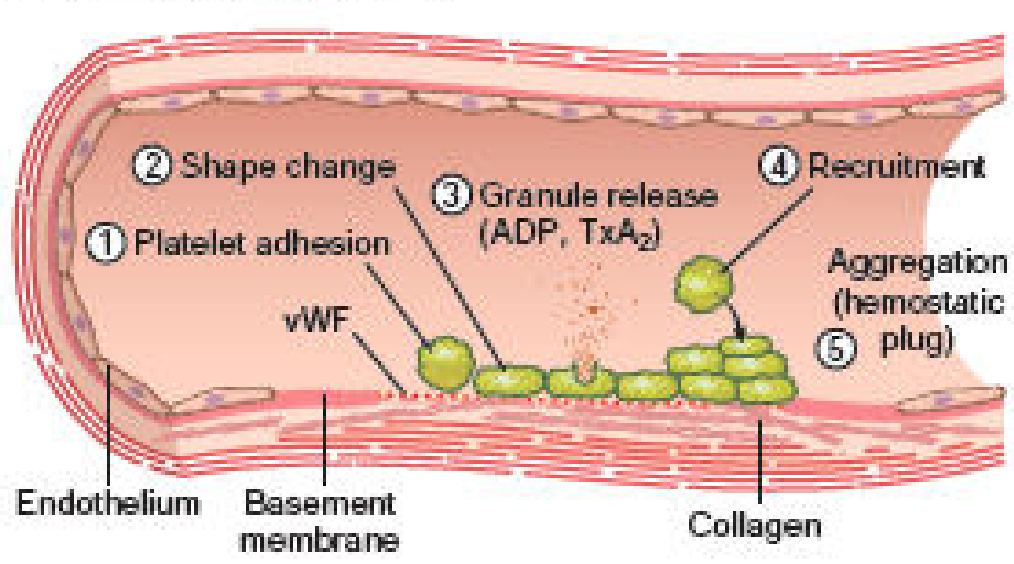


- ***Primary haemostasis involves the binding of platelets to exposed collagen in the sub endothelium of damaged vessels.***

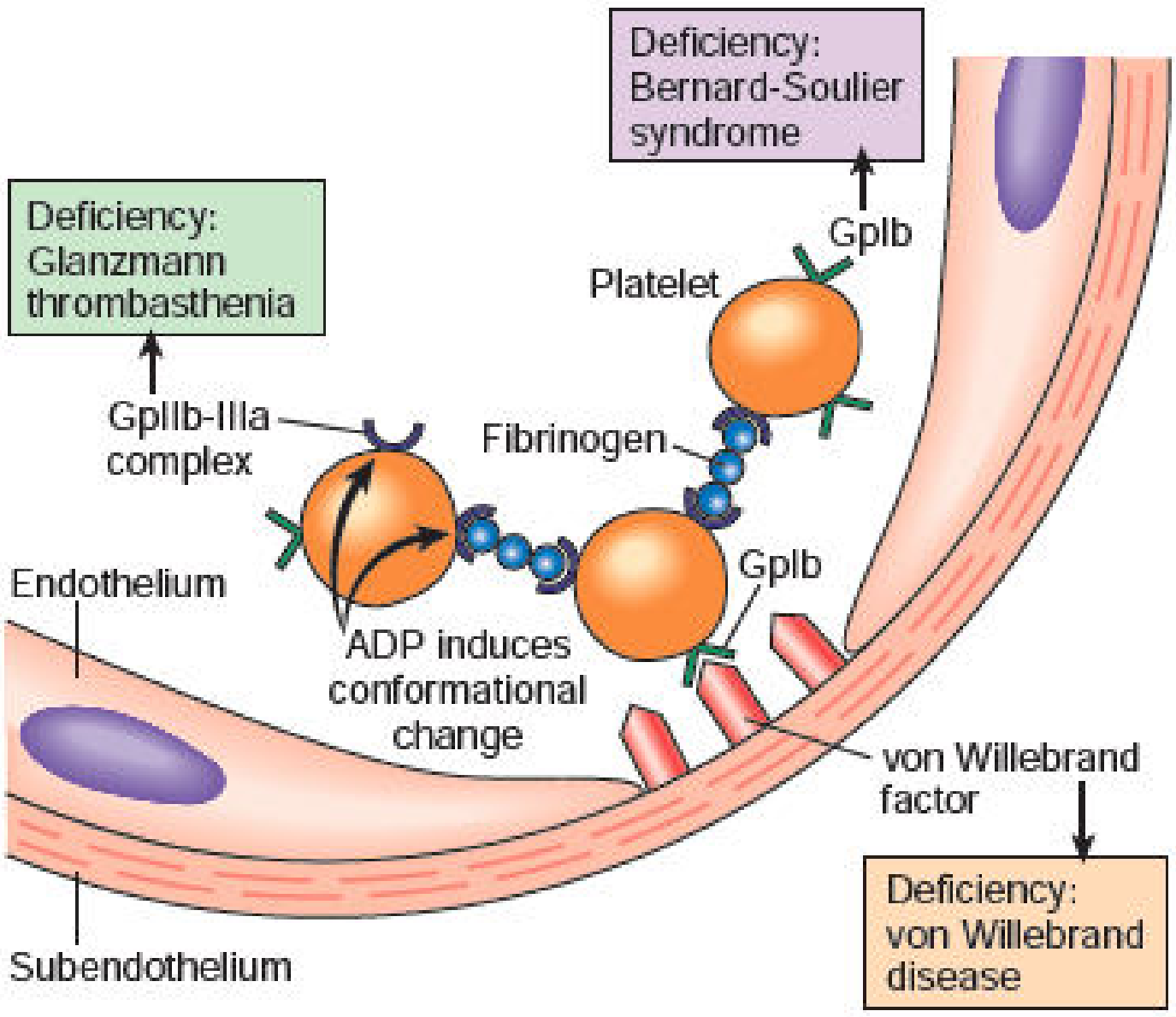
- ***Secondary haemostasis is the process of activation of coagulation factors leading to the production of thrombin.***



(A) → After vascular injury, local neurohumoral factors induce a transient vasoconstriction.



(B) → Platelets bind via glycoprotein Ib (GpIb) receptors to von Willebrand factor (vWF) on exposed extracellular matrix (ECM) and are activated, undergoing a shape change and granule release. Released ADP & thromboxane A2 (TxA2) induce additional platelet aggregation through platelet GpIIb -IIIa receptor binding to fibrinogen, and form the primary hemostatic plug.

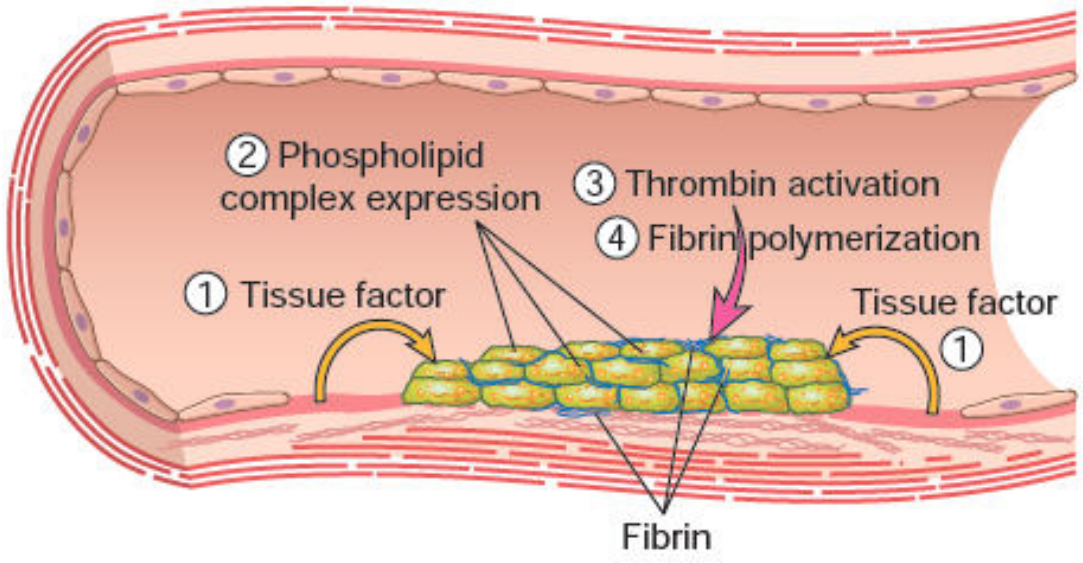


Platelet adhesion and aggregation-

Von Willebrand factor functions as an **adhesion bridge** between subendothelial collagen and the glycoprotein Ib (GpIb) platelet receptor. **Aggregation** occurs by fibrinogen bridging GpIIb-IIIa receptors on different platelets.

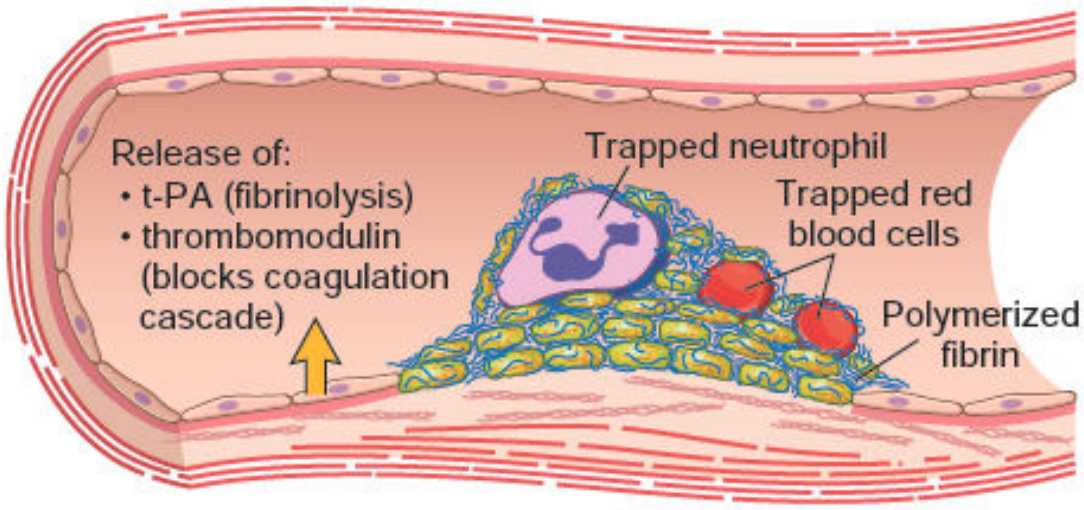
Congenital deficiencies in the various receptors or bridging molecules lead to different diseases.

C. SECONDARY HEMOSTASIS



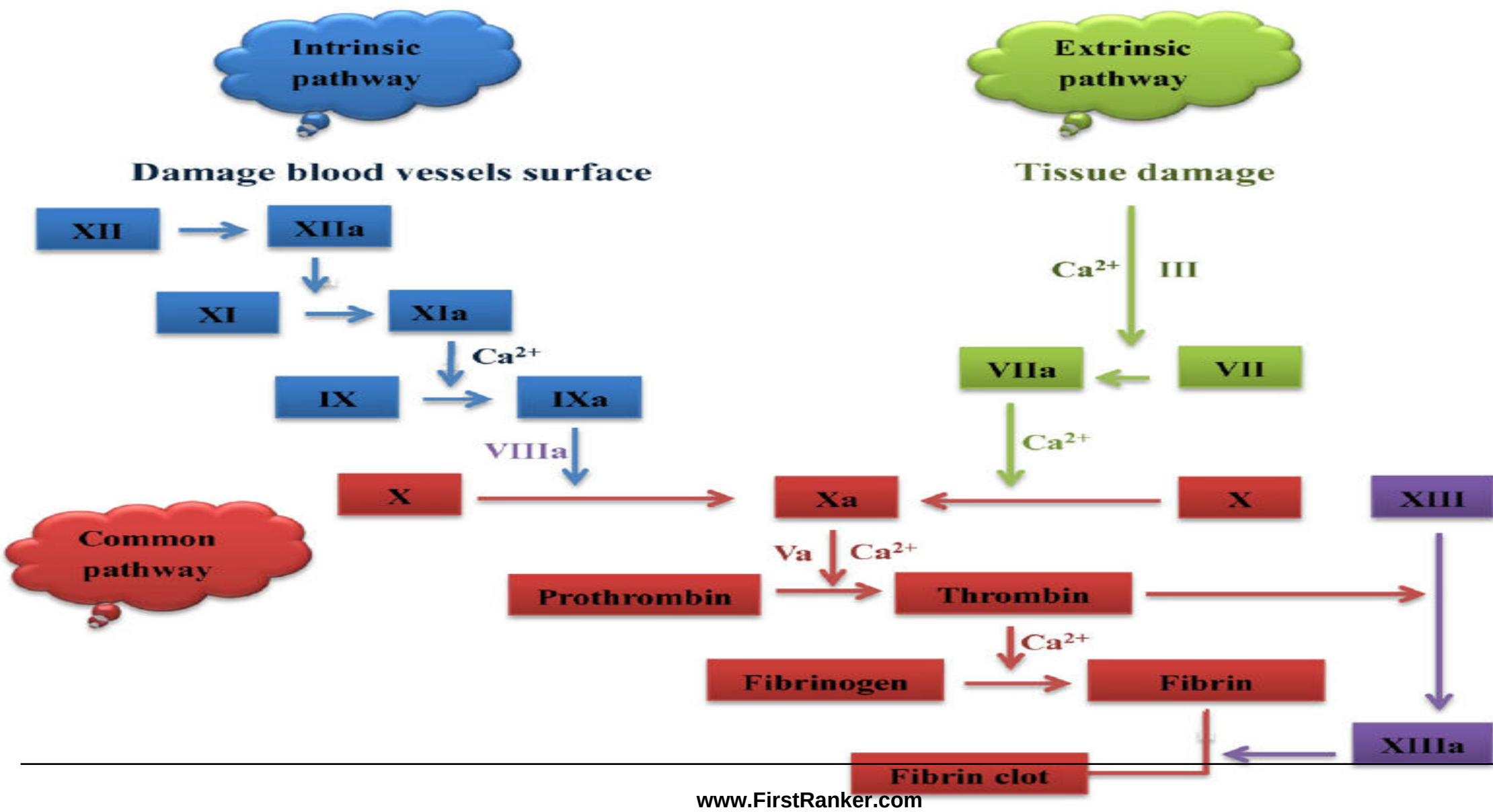
(C) → Local activation of the coagulation cascade (involving tissue factor and platelet phospholipids) results in fibrin polymerization, "cementing" the platelets into a definitive secondary hemostatic plug.

D. THROMBUS AND ANTITHROMBOTIC EVENTS



(D) → Counterregulatory mechanisms, mediated by tissue plasminogen activator (t-PA, a fibrinolytic product) and thrombomodulin, confine the hemostatic process to the site of injury

SIMPLIFIED DIAGRAM OF COAGULATION CASCADE:-



PROCOAGULANT FACTORS :-

FACTOR NUMBER	FACTOR NAME	NATURE	SOURCE
I	Fibrinogen	Plasma protein	Liver
II	Prothrombin	Plasma protein	Liver*
III	Tissue factor (TF)	Plasma membrane glycoprotein	Tissue cells
IV	Calcium ions (Ca^{2+})	Inorganic ion	Plasma
V	Proaccelerin	Plasma protein	Liver, platelets
VI†			
VII	Proconvertin	Plasma protein	Liver*
VIII	Antihemophilic factor (AHF)	Plasma protein	Liver, lung capillaries
IX	Plasma thromboplastin component (PTC)	Plasma protein	Liver*
X	Stuart factor	Plasma protein	Liver*
XI	Plasma thromboplastin antecedent (PTA)	Plasma protein	Liver
XII	Hageman factor	Plasma protein; activated by negatively charged surfaces (e.g., glass)	Liver
XIII	Fibrin stabilizing factor (FSF)	Plasma protein	Liver, bone marrow

PROCOAGULANT FACTORS.. Cont'd.. :-

High-molecular-weight kininogen	HMWK Fitzgerald factor	Plasma protein stored in platelets Kallikrein clips bradykinin from HMWK
Plasma prekallikrein	Fletcher factor Plasma kallikrein precursor	Plasma protein
Plasma kallikrein		Serine protease Kallikrein clips bradykinin from HMWK
von Willebrand factor	vWF	Plasma glycoprotein made by endothelial cells and megakaryocytes Stabilizes factor VIIIa Promotes platelet adhesion and aggregation

ANTICOAGULANT FACTORS:-

NAME	ALTERNATE NAMES	PROPERTIES
Anticoagulant Factors		
Tissue factor pathway inhibitor	TFPI	Protease inhibitor produced by endothelial cells GPI linked to cell membrane
Antithrombin III	AT III	Plasma protein Serine protease inhibitor, member of serpin family Inhibits factor Xa and thrombin, and probably also factors XIIa, XIa, and IXa Heparan and heparin enhance the inhibitory action
Thrombomodulin (cofactor)		Glycosaminoglycan on surface of endothelial cell Binds thrombin and promotes activation of protein C
Protein C	Anticoagulant protein C Autoprothrombin IIA	Plasma protein Synthesis in liver requires vitamin K*
Protein C_a	Activated protein C	Serine protease Disulfide-linked heterodimer
Protein S (cofactor)		Plasma protein Synthesis in liver requires vitamin K* Cofactor for protein C

Bleeding disorder

Bleeding disorders can be due to

Blood vessel anomalies **Platelet abnormalities** **Coagulation disorders**

DISORDERS OF VESSEL WALL:-

HEREDITARY:-

1) Hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu disease)
2) Ehler Danlos Syndrome

ALLERGIC:-

1) Henoch–Schönlein purpura (HSP)
2) Leucocytoclastic angitis

ATROPHIC:-

1) Senile purpura
2) Scurvy

MISCELLANEOUS:-

1) Simple easy bruising
2) Amyloidosis
3) Infections

PLATELET DISORDERS.. Cont'd:-

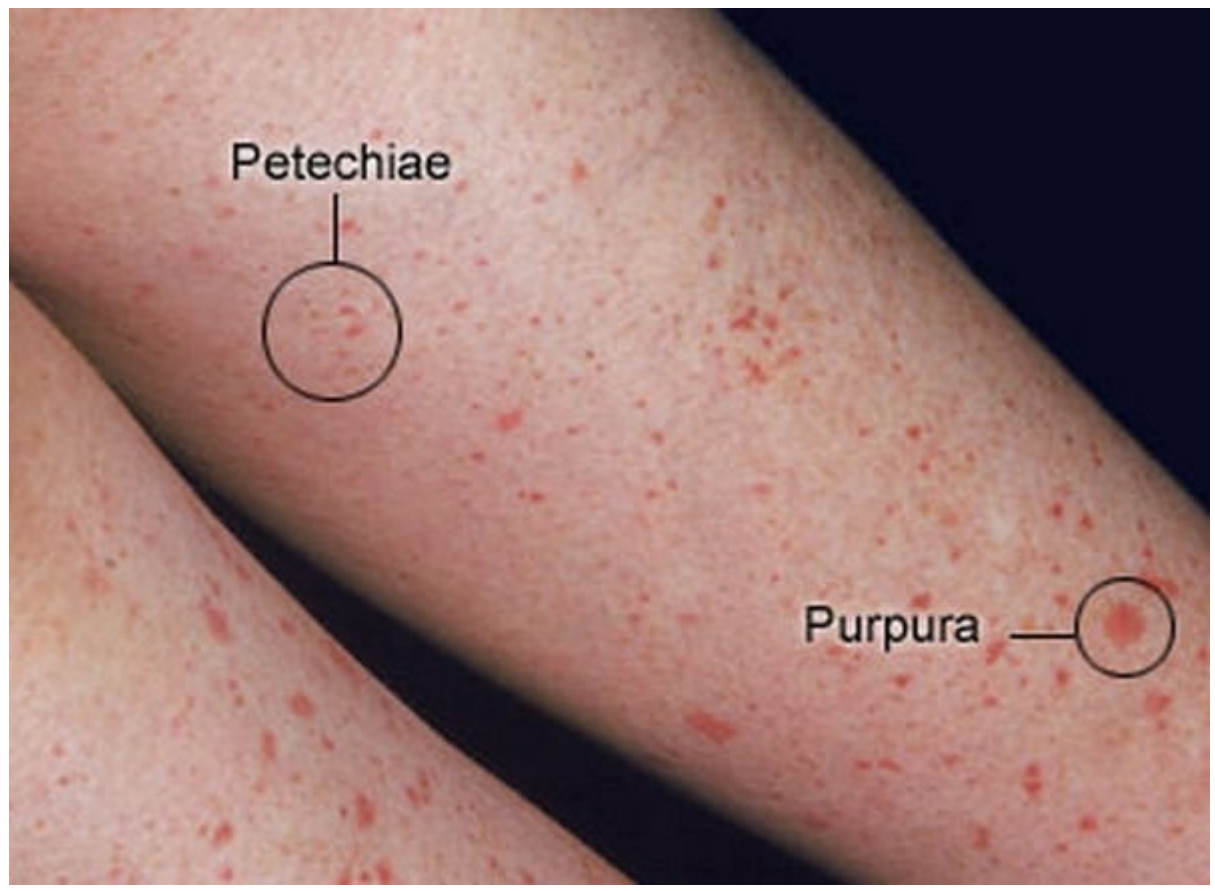
DISORDERS OF PLATELET NUMBER #		
DECREASED PRODUCTION	INCREASED DESTRUCTION	PERIPHERAL POOLING
PURE AMEGAKARYOCYTIC THROMBOCYTOPENIA	**IMMUNE**	**Hypersplenism**
BONE MARROW FAILURE aplastic anemia MDS megaloblastic anemia infiltration of marrow	**Primary** acute ITP chronic ITP Evan's syndrome Alloimmune	
HYPOPLASIA OF MEGAKARYOCYTES Alcohol Viral infection Chemotherapy	**Secondary** infections drugs SLE pregnancy transfusion	
INEFFECTIVE ERYTHROPOEISIS	**NON IMMUNE** TTP HUS Dengue	

DISORDERS OF PLATELET FUNCTION	
INHERITED	ACQUIRED
Bernard soulier syndrome Glanzmann thrombasthenia Storage pool def Gray platelet synd Wiskott Aldrich Abnormal release rn Hermansky Pudlak Chediak Higashi	uremia paraproteinemia Drugs Aspirin NSAIDs Penicillin myeloproliferative disorders

DISORDERS OF COAGULATION:-

INHERITED	ACQUIRED
HEMOPHILIA A	DIC
HEMOPHILIA B	LIVER DISEASE
vWD	HDN
DISORDERS OF FIBRINOGEN- HEREDITARY AFIBRINOGENAEMIA HYPOFIBRINOGENAEMIA DYSFIBRINOGENAEMIA	Nephrotic Syndrome
FXIII deficiency	APLS
FV deficiency	HEPARIN OR ORAL ANTICOAGULANT THERAPY
	VIT K DEFICIENCY
	MASSIVE TRANSFUSION OF STORED BLOOD

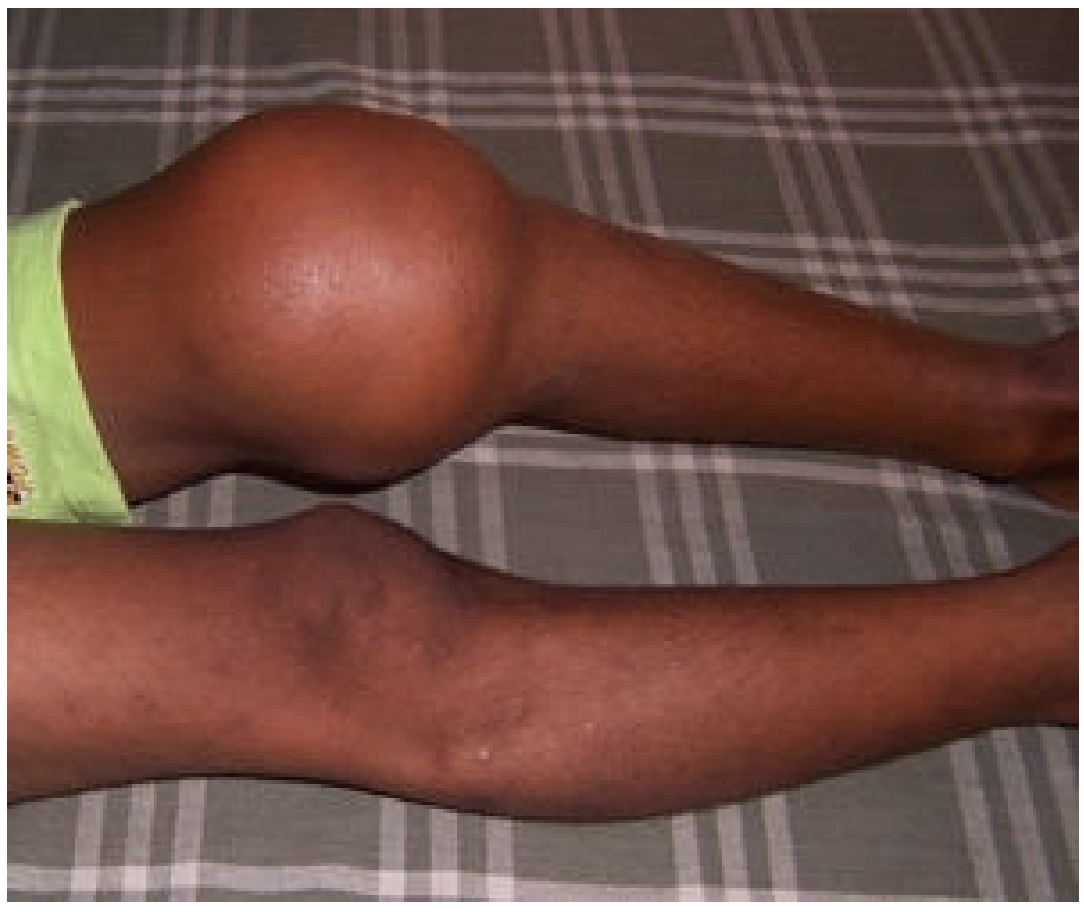
Clinical evaluation.. Cont'd:-



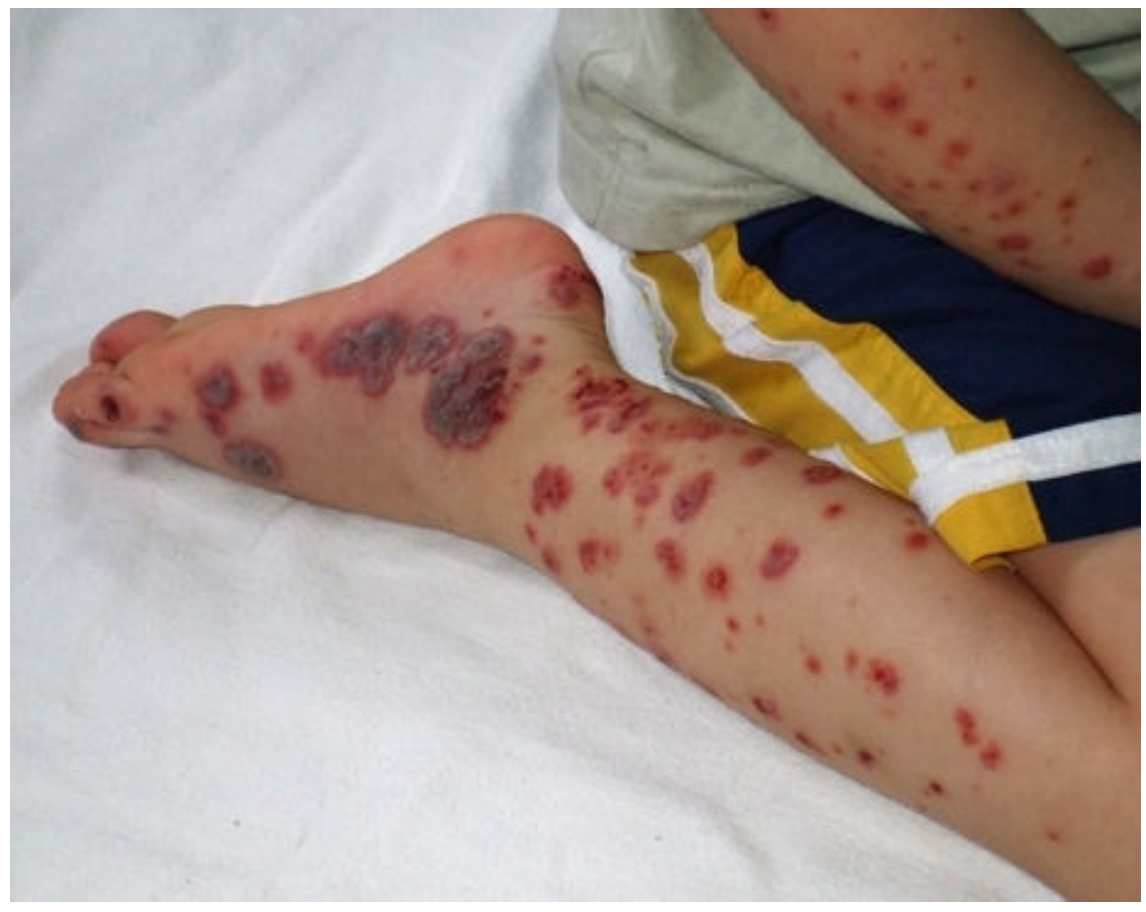
.

Petechiae → <3 mm, Purpura→ 0.3–1 cm (3–10 mm), ecchymoses→ >1 cm.

Clinical evaluation.. Cont'd:-



Hemarthrosis in a case of Hemophilia



Purpura in a case of ITP

Von willebrand Disease

- One of the Most Common inherited disorders of bleeding
- AD disease with gene located on 12 th chromosome
- vwf synthesize in endothelium, platelet and megakatyocytes
- vwf facilitate platelet adhesion to subendothelial collagen

C/F – Spontaneous bleeding from mucus membrane,
Excessive bleeding from wounds / gums
Menorrhagia
>20 variants reported

Type1(50% activity) & 3(no activity)
Reduced vWF

Type 2
Qualitative defects

Lab Findings

- Prolonged BT
- (Normal) platelet count
- Deficient Ristocetin aggregation
- Prolonged PTT

Treatment

- cryoprecipitate

HEMOPHILIA – A
(F – VIII deficiency)

Most Common hereditary disease
Reduced activity of F – VIII
X – linked recessive trait
30% of patients have no positive family history

<1% of normal F-VIII activity – Severe disease

2 – 5% of normal F-VIII activity – Moderate disease

6 – 50% of normal F-VIII activity – Mild disease

Clinical /Features:

normal hemostasis require 25% factor VIII activity

Symptomatic patients mostly have < 5% factor VIII activity

Easy bruising

Massive Hemorrhage after mild trauma / operation

Joint bleeding – Haemarthrosis – Deformities

Lab Features

- Bleeding Time - Normal
- Prothrombin Time - Normal
- Platelet Count - Normal
- APTT - Increased
- Diagnosis can be confirmed by F-VIII assay.

Therapy

F-VIII Infusion

15% of severely affected patients –developed Antibodies against F - VIII

HEMOPHILIA – B

Severe Factor - IX deficiency

X – linked recessive

PT – Normal

APTT – Increased

Factor assay is must to differentiate between Hemophilia A & Hemophilia B

Screening tests for primary hemostasis are -

I. Bleeding time- Assesses adequate functioning of platelets and blood vessels

II. Peripheral blood smear examination

III. Platelet count

IV. Mean Platelet volume

V. Reticulated platelets

VI. Platelet function analysis

VII. Tests for Vessel wall disorder

Tests for Vessel wall disorder

HESS` CAPILLARY FRAGILITY TEST:

- Cuff is wrapped in upper arm and pressure is maintained midway b/w systolic and diastolic BP for 15 minutes, 4 cm below the elbow joint, a circle of 2.5 cm diameter is drawn on the anterior aspect of forearm.
- Upto 10 new hemorrhagic spots are normal. But >20 new spots are always pathological.
- This is positive in increased capillary fragility, ITP.

Screening tests for secondary hemostasis are -

I. **Clotting time**
II. **Prothrombin time (PT) and Activated partial thromboplastin time (aPTT)**
III. **Thrombin Time (TT)**

Collection of blood for coagulation studies

- The anticoagulant used for coagulation studies is trisodium citrate (3.2%), with anticoagulant to blood proportion being 1:9.

Clotting Time

- This is a crude test and is now replaced by activated partial thromboplastin time.
- Prolongation of clotting time only occurs in severe deficiency of a clotting factor and is normal in mild or moderate deficiency.

PROTHROMBIN TIME(PT)

- **PT assesses coagulation factors in extrinsic pathway (F VII) and common pathway.**
- **Principle:- Tissue thromboplastin and calcium are added to platelet poor plasma and clotting time is determined.**

CONCEPT OF INR

1.The international normalized ratio **(INR)** was introduced **in an attempt to standardize the PT.**

2.Calculation ~ INR = [PT (patient) / PT (Control)]^{ISI}

The INR has no units (it is a ratio)

**ISI, or international sensitivity index is a function of the thromboplastin reagent.

**** NORMAL RANGE→ PT 11-16 seconds INR 0.9 – 1.1.**

Uses of PT

1. To monitor patients who are on oral anticoagulant therapy
2. To assess liver function
3. Detection of vitamin K deficiency
4. To screen for hereditary deficiency of coagulation factors

Causes of prolongation of PT

1. Treatment with oral anticoagulants
2. Liver disease
3. Vitamin K deficiency
4. Disseminated intravascular coagulation

ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT)

Significance

- Reflects efficiency of Intrinsic and Common pathway.

Principle

The test measures the clotting time of plasma after the activation of contact factors (Kaolin/Silica/Ellagic acid) and the addition of phospholipid and $CaCl_2$, but without added tissue thromboplastin.

So it indicates the overall efficiency of the Intrinsic pathway.

Normal range

26 to 40 seconds.

Uses of APTT:-

1. Screening for hereditary disorders of coagulation
2. To monitor heparin therapy
3. Screening for circulating inhibitors of coagulation

aPTT is prolonged in:-

1.Inherited deficiencies of factor VIII (Hemophilia A) and Factor IX (Hemophilia B)

2.Non specific inhibitor antibodies against F VIII e.g. Lupus inhibitor (Don't act directly but block interaction of FVIII with other clotting factors)

3.DIC

4.Heparin

(→Inhibits factor XII, XI and X through antithrombin III & Heparin therapy is monitored through aPTT)

5. Vit K deficiency

6.Massive transfusion of plasma depleted stored blood.

THROMBIN TIME(TT)

Significance:-

- Asses the final step of coagulation i.e. conversion of fibrinogen to fibrin in presence of thrombin.
- Bypasses Extrinsic & Intrinsic pathway.

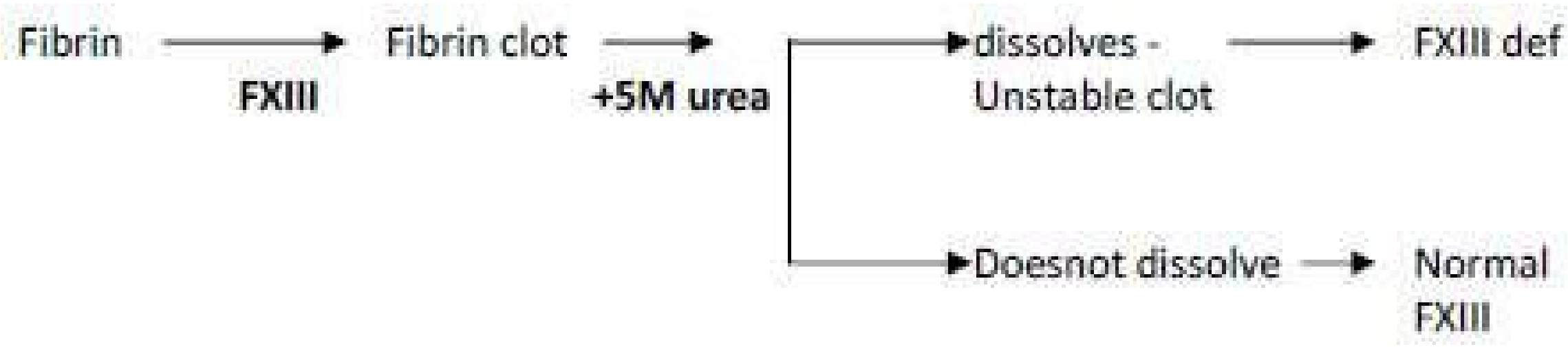
Causes of prolonged TT

1. Disorders of fibrinogen-
   i) Afibrinogenaemia
   ii) Hypofibrinogenaemia
3. Chronic liver disease

FXIII Qualitative assay (Urea clot lysis test)

- Done when all other tests for hemostasis are normal.
- FXIII provides stability to clot formed.

Method:-



Summary of Approach to Bleeding Disorders