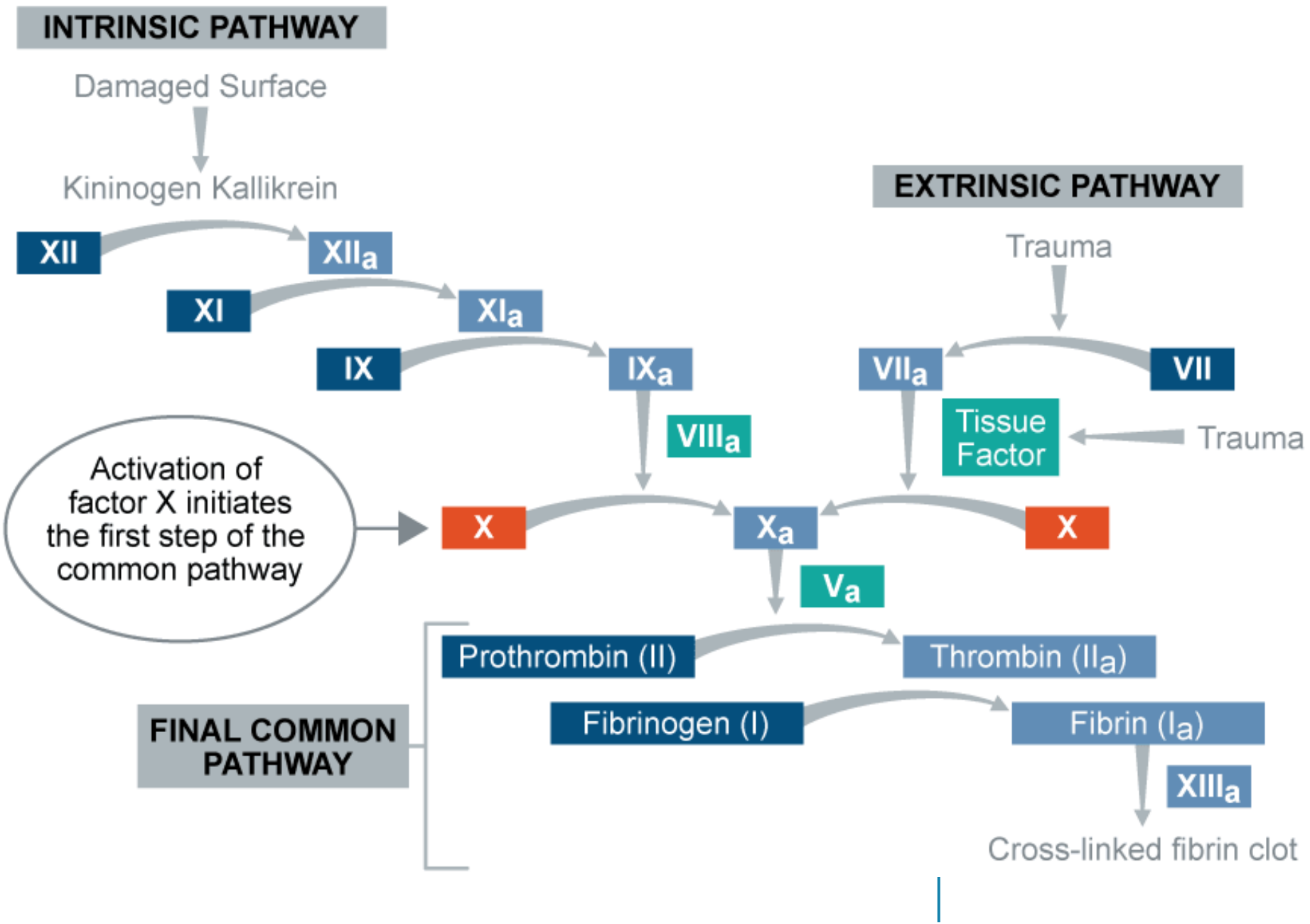
COAGULATION DISORDERS

Dr. ZAHRAA ALQAISI


INTRINSIC PATHWAY
Damaged Surface
Kininogen Kallikrein
XII
XIIa
XI
XIa
IX
IXa
VIIIa
EXTRINSIC PATHWAY
Trauma
VIIa
VII
Tissue Factor
Trauma
Activation of factor X initiates the first step of the common pathway
X
Xa
X
Va
FINAL COMMON PATHWAY
Prothrombin (II)
Thrombin (IIa)
Fibrinogen (I)
Fibrin (Ia)
XIIIa
Cross-linked fibrin clot

CLASSIFICATION

1. **Hereditary Coagulation Disorder**

   These inherited plasma coagulation disorders are due to qualitative or quantitative defect in single coagulation factor.

   a. *Sex Linked (X) Disorders* : e.g. Classical haemophilia or haemophilia A, Christmas disease or haemophilia B
   b. *Autosomal Disorders* : e.g. von Willebrand's disease

2. **Acquired Coagulation Disorder**

   These are characterized by deficiency of multiple coagulation factor.

   a. Vitamin K deficiency
   b. Coagulation disorder of liver disease
   c. Disseminated intravascular coagulation DIC
   d. Fibrinolytic defects

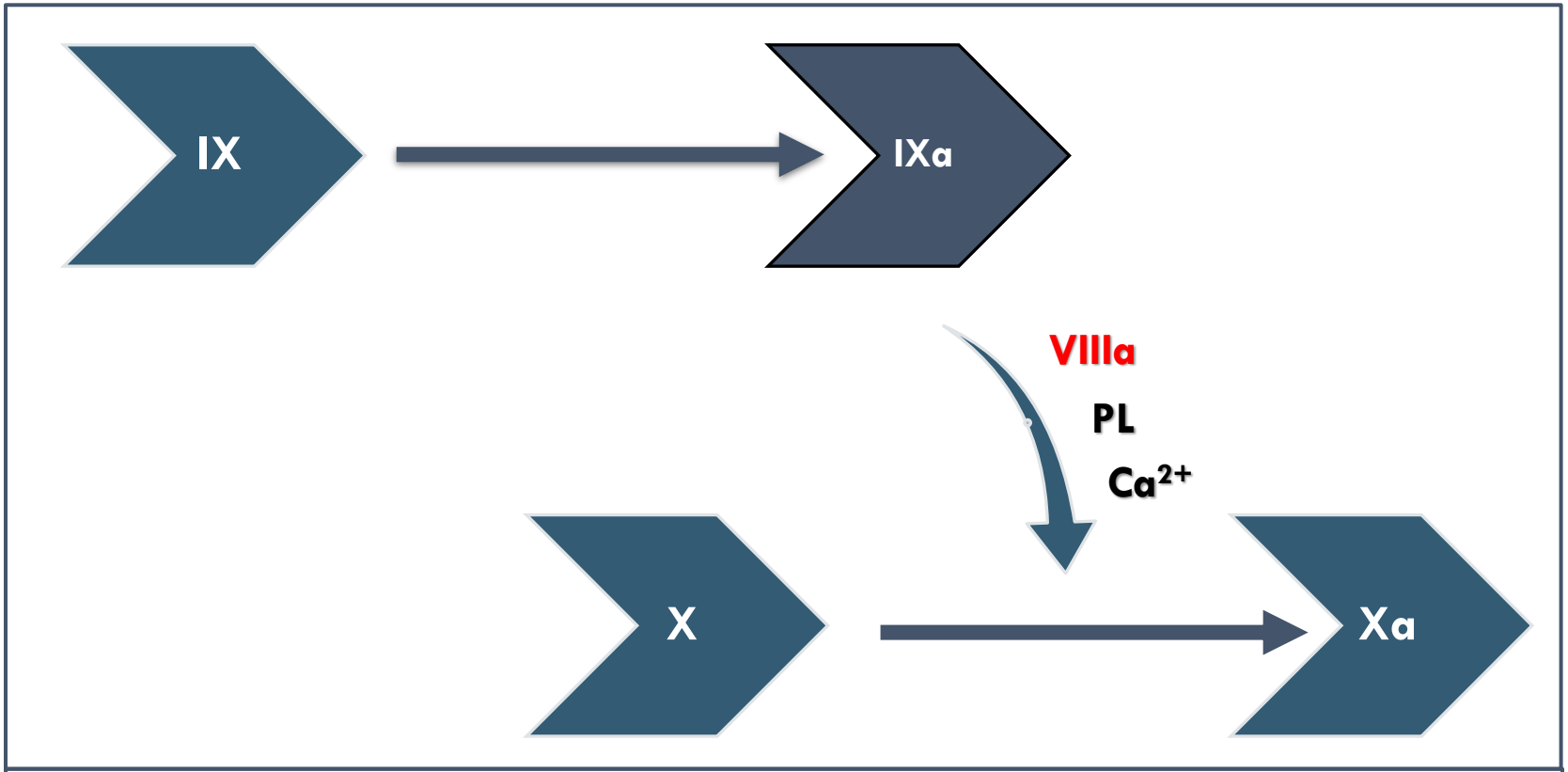
INHERITED COAGULATION DISORDERS

- Most important is **Hemophilia A** : Due to inherited deficiency of Factor VIII.
- Probably the most frequent, but clinically less significant is **vonWillebrand's Disease**, due to deficiency of vonWillebrand's factor.
- Next in importance is **Hemophilia B (Christmas Disease)** due to sex-linked inherited deficiency of Factor IX.
- Other inherited coagulation defects are much less frequent and include : Fibrinogen(Factor I) Deficiency, Factor VII, Factor X etc.

HEMOPHILIA A

- Its is the **second most common** cause, sex linked inherited disorder characterized by deficiency of factor VIII.
- **Caused by either:**
  - **Quantitative reduction** in factor VIII (in 90% of cases) OR
  - **Qualitative** defect :Normal or increased level of factor VIII with **reduced activity** (in 10% of cases).
- Factor VIII is synthesized in hepatocytes. In the intrinsic coagulation pathway factor IXa complexes with factor VIIIa, this complex in the presence of platelets, PL and Ca2+ activates factor X to Xa.

HAEMOPHILIA A

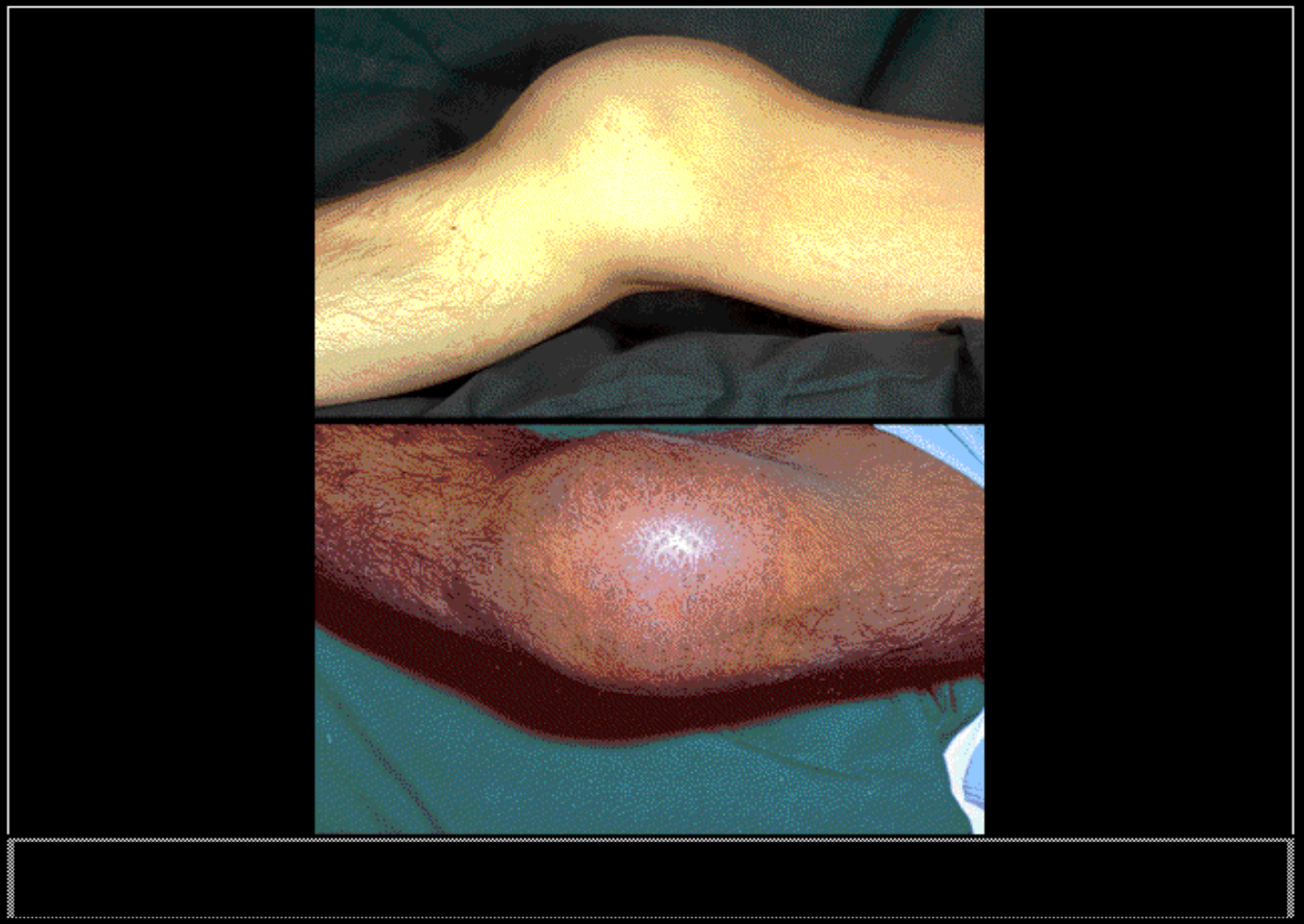


Disruption of the Intrinsic Coagulation Pathway (Due to the absence of activated Factor VIII)

Clinically :

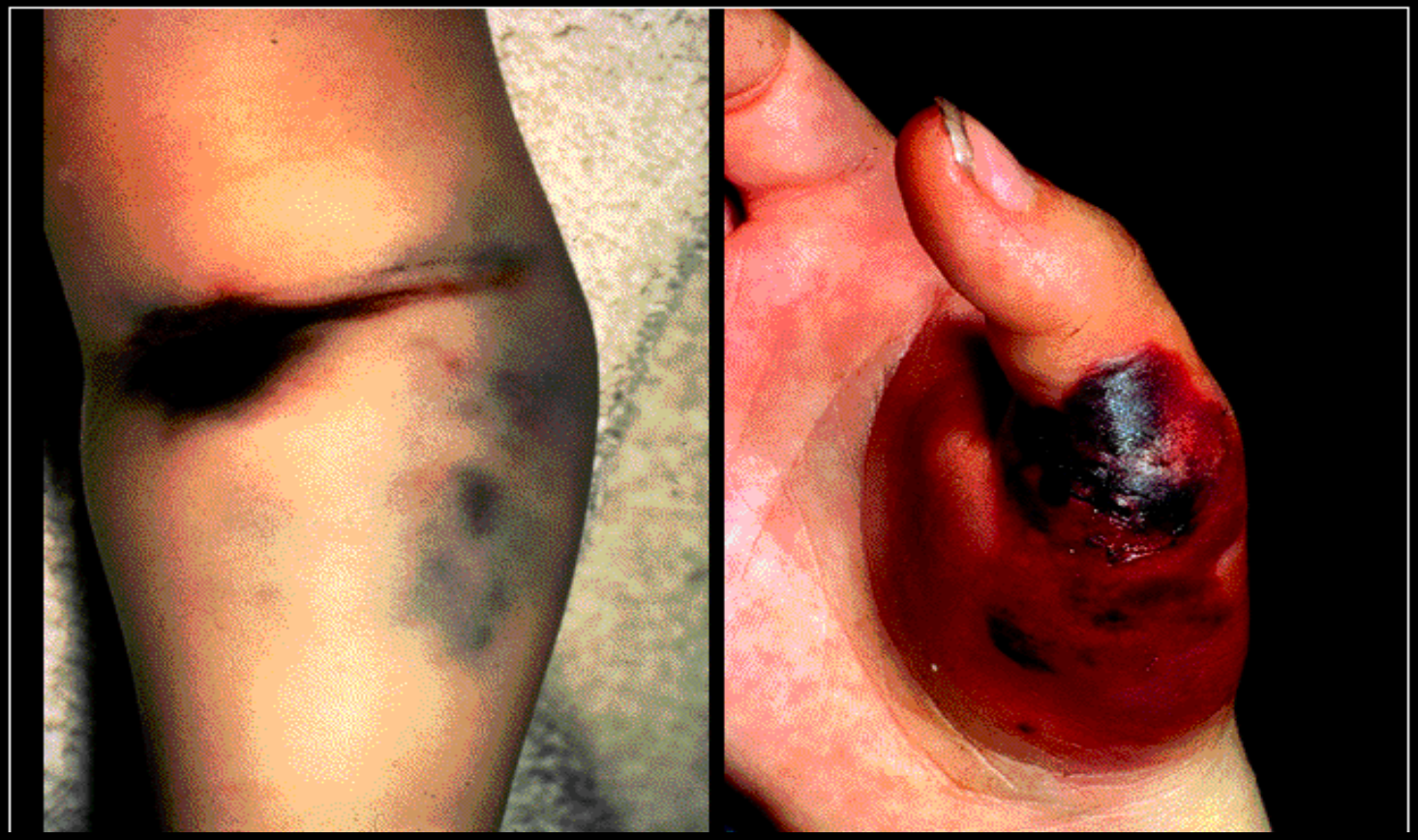
- **Males** are affected.
- Features start usually when the infant starts to **crawl or walking**.
- Symptoms are appear when factor VIII activity is reduced to **less than 25%.**
- Patient suffers bleeding for hrs. to days and severity is based on plasma concentration of factor VIII activity
- One of the main features is **Hemarthrosis** (bleeding into joints).
- Bleeding into muscles, S/C tissue, after any injury or surgery, painless hematuria, GI bleeding also may be seen.

HEMOPHILIA (HEMARTHROSIS)

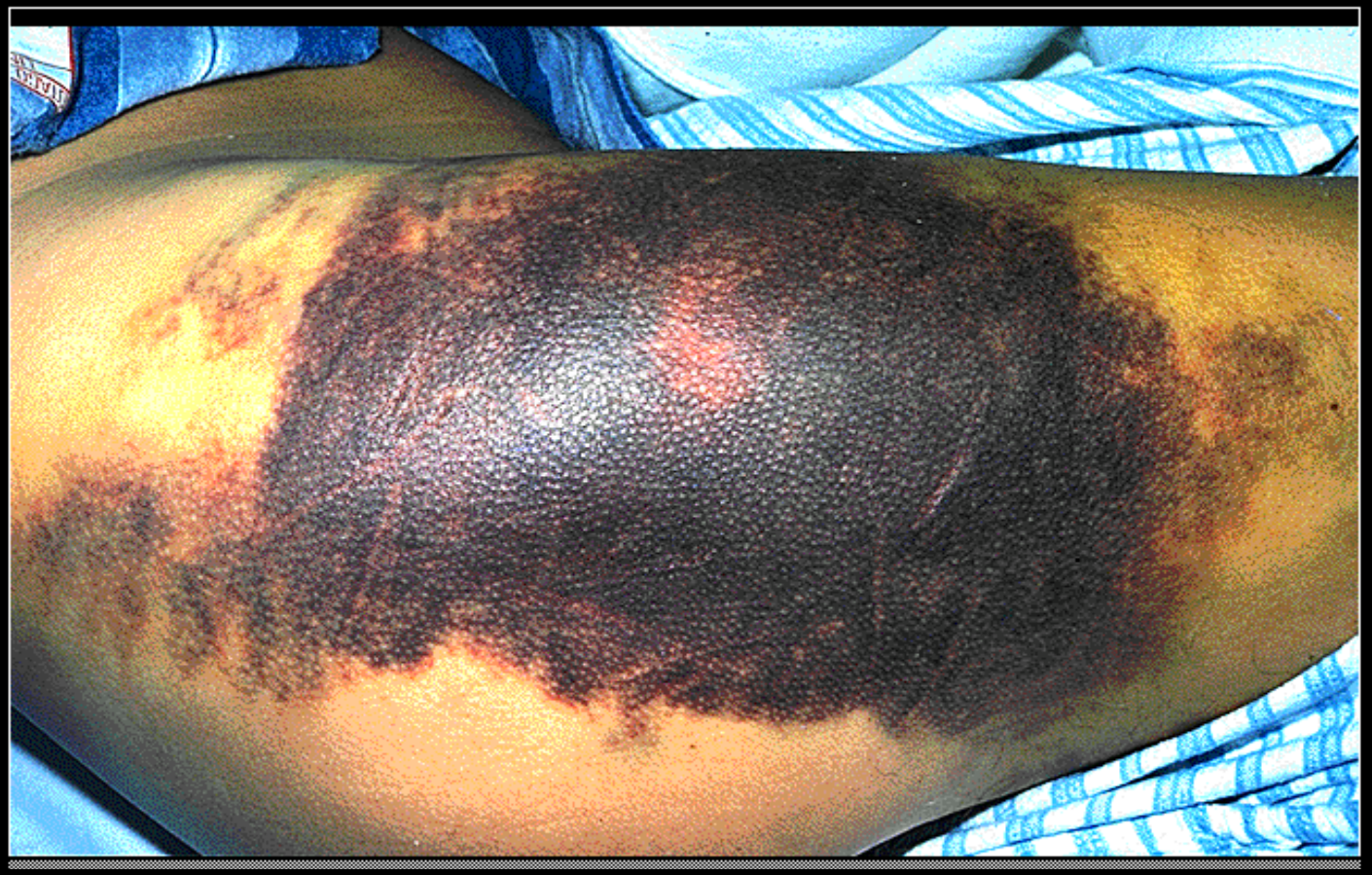


Knee Joint

HEMATOMAS



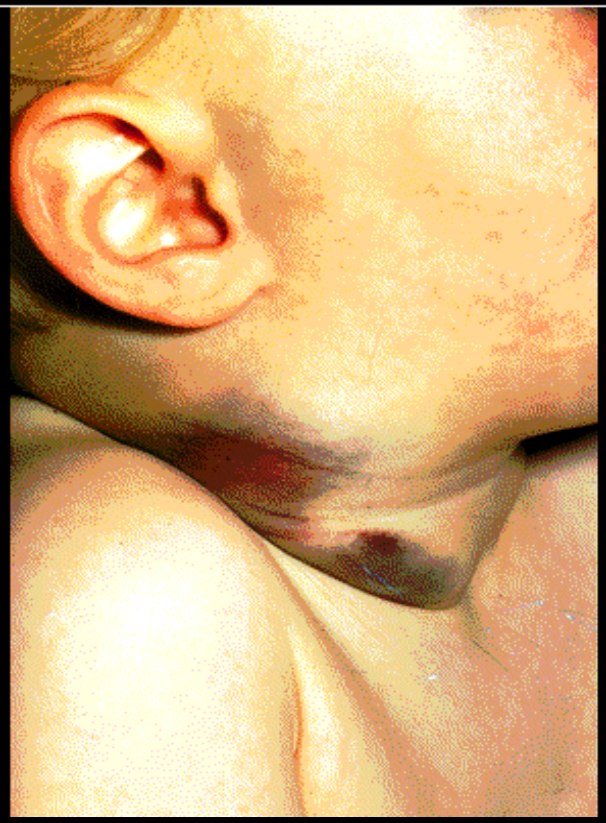
Hemophilia



Hematoma

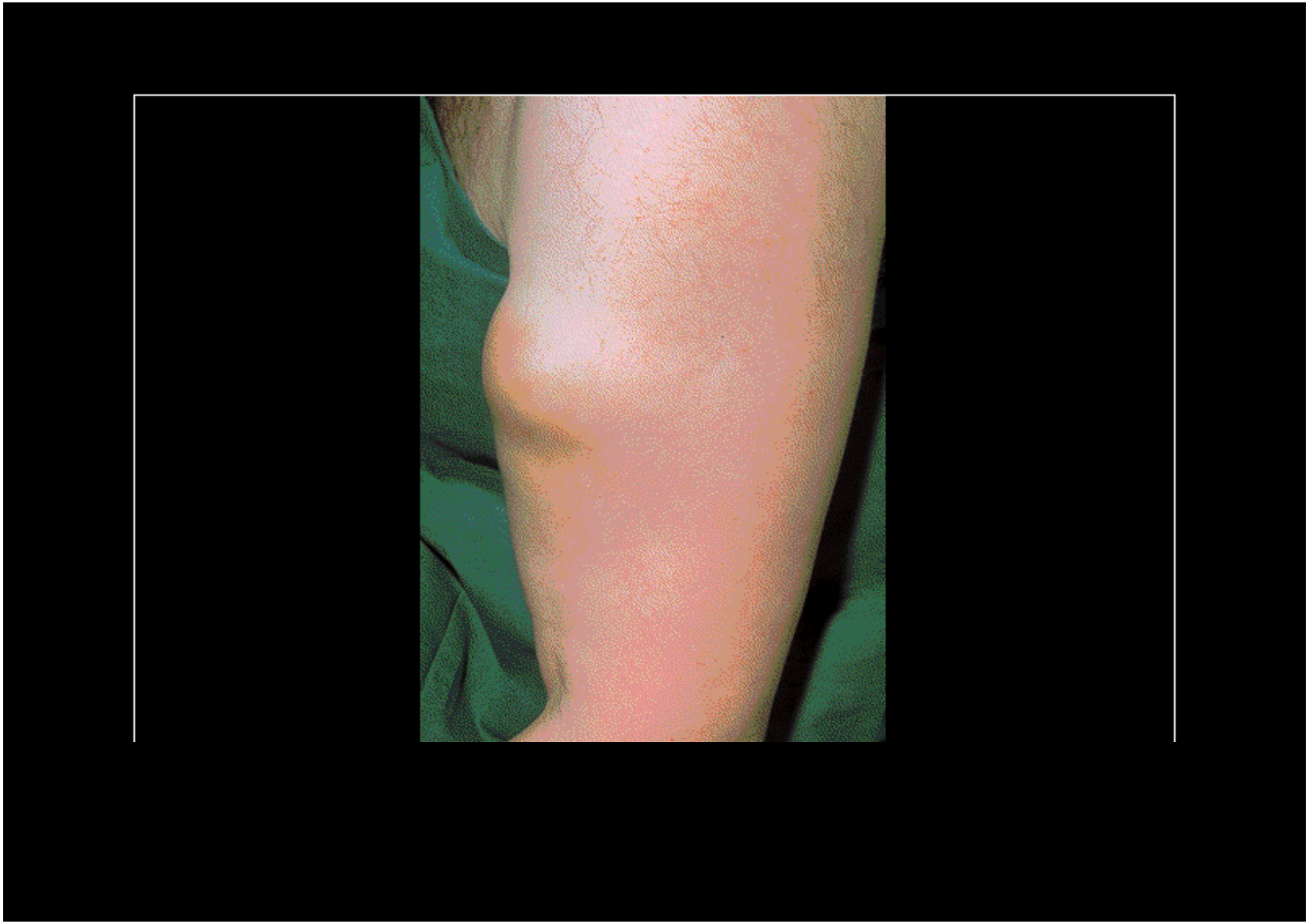
Hemophilia

Hemophilia



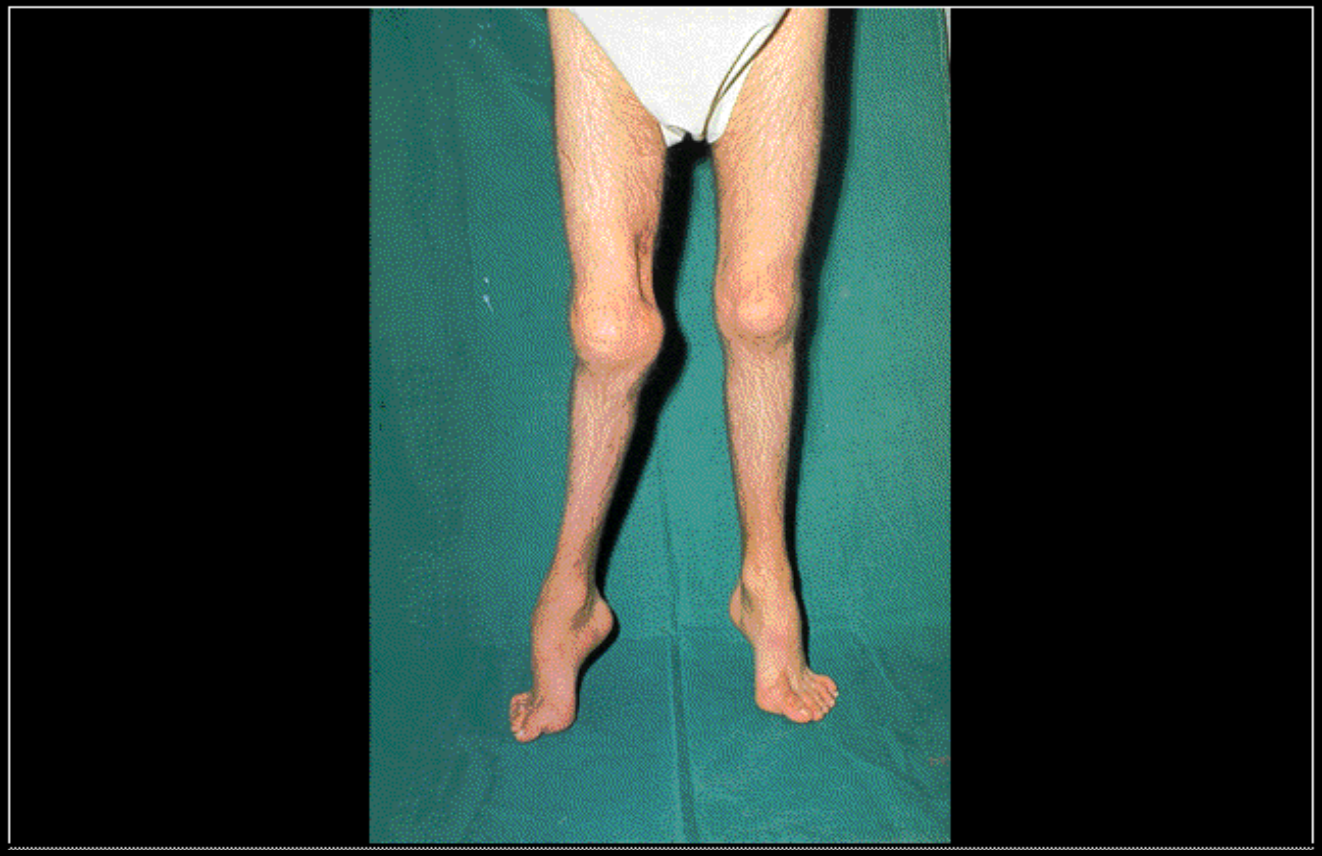
S/C HEMATOMA

Hemophilia

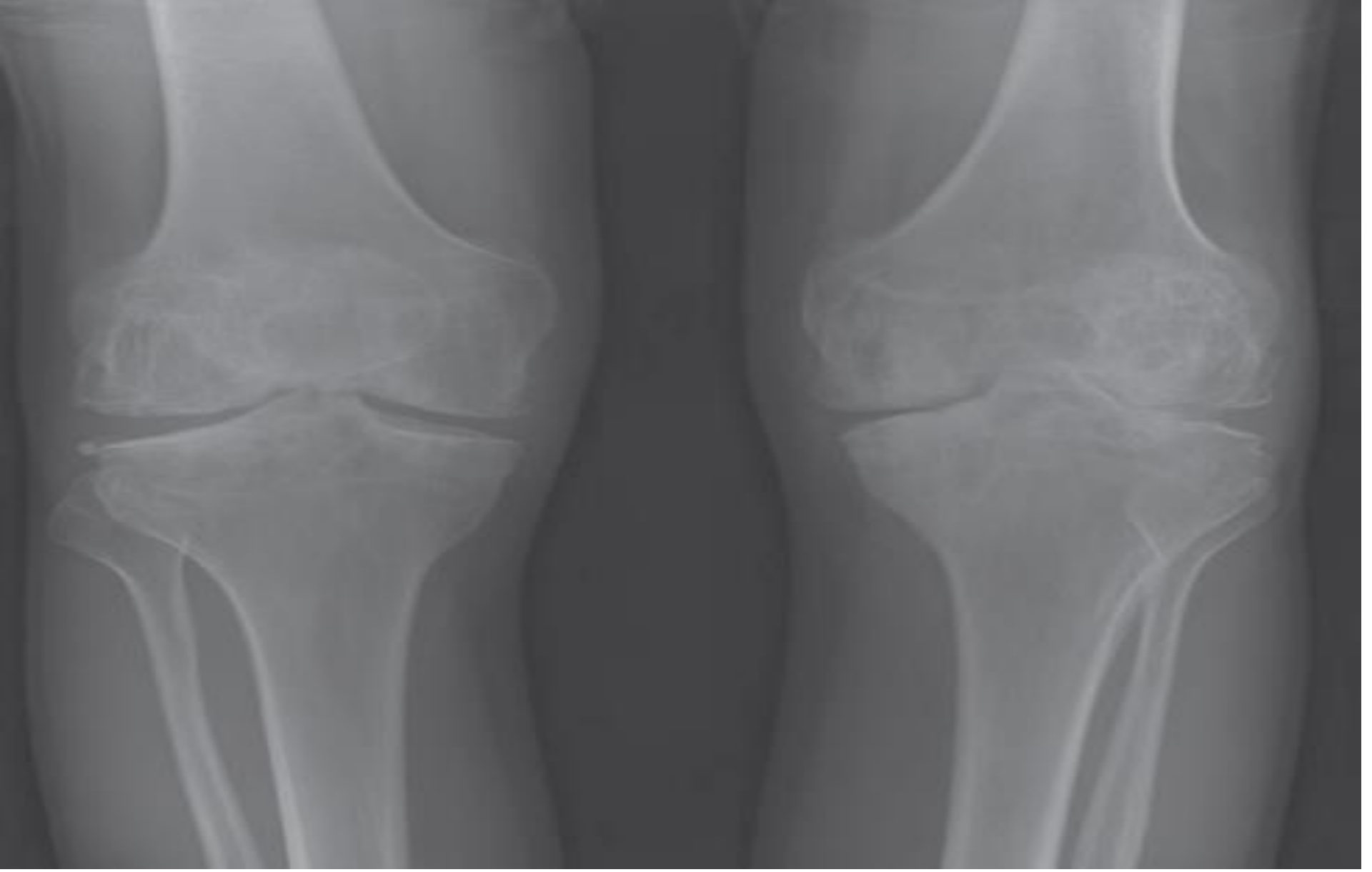


Bleeding into biceps muscle -Pseudotumor

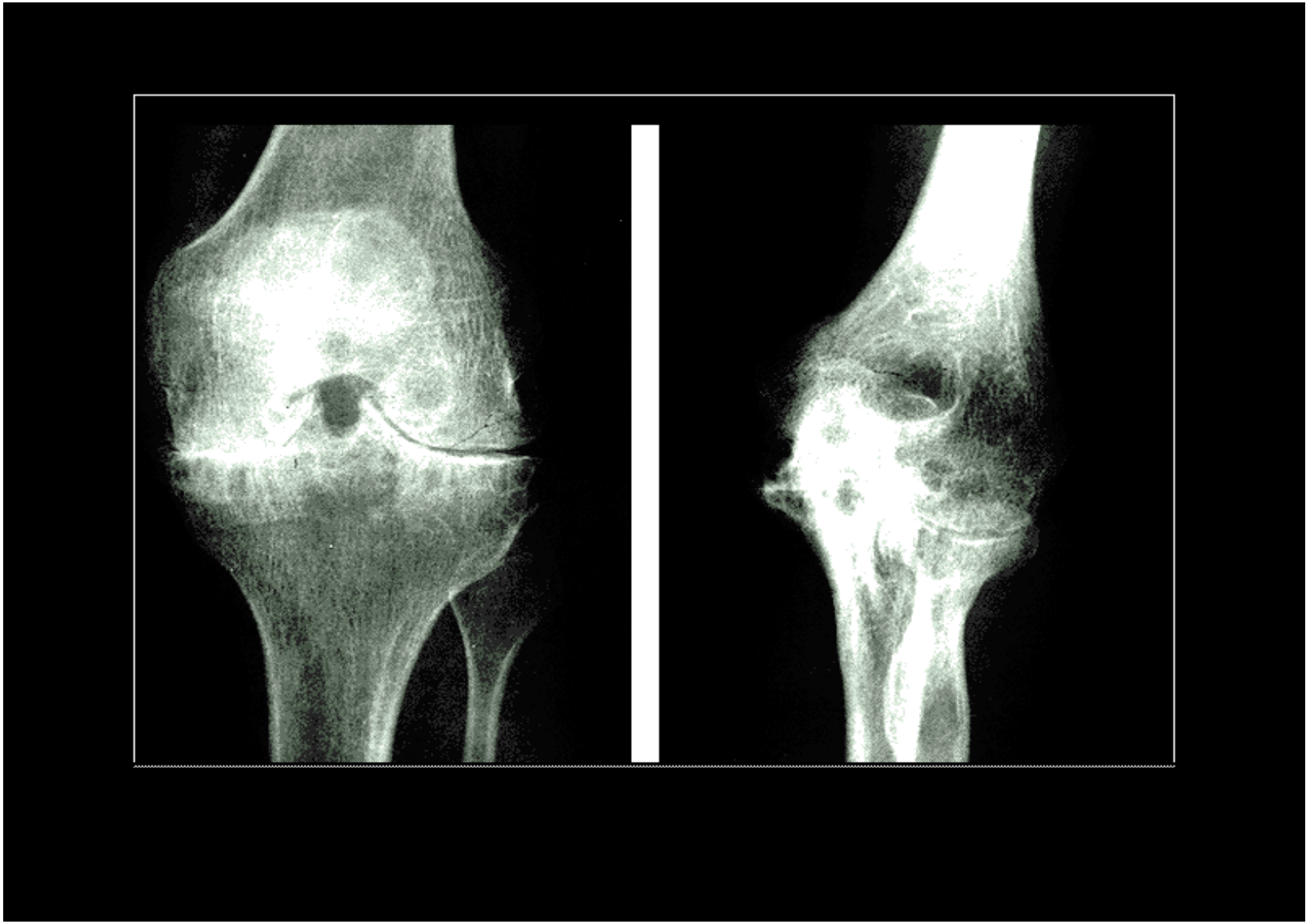
Hemophilia



Long term sequels of hemophilia : Deformities due to recurrent hemarthrosis and permanent joint damage and muscle atrophy



Haemophilia A: X-ray of the knee joints shows destruction and narrowing of the left joint space.

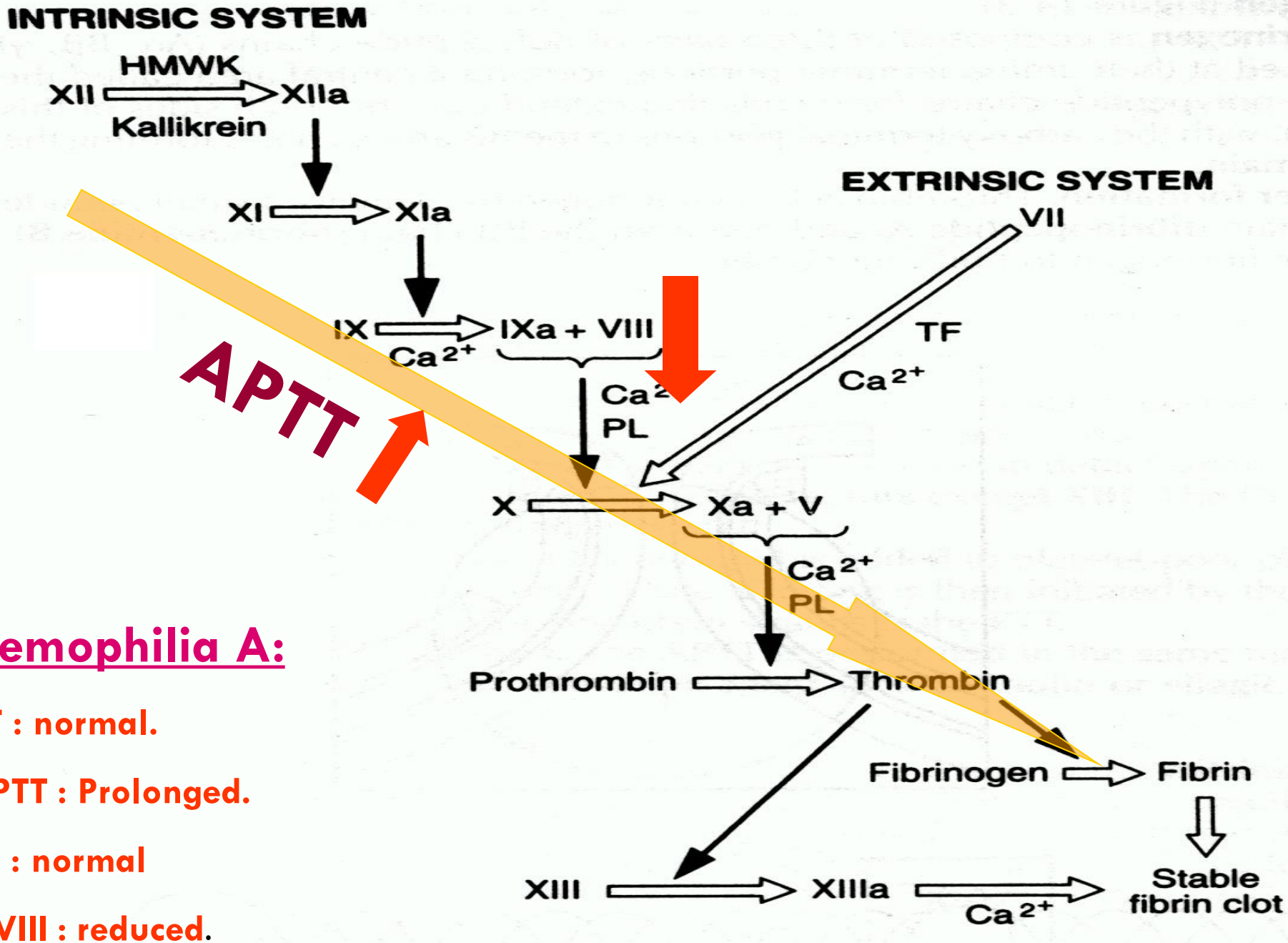


Long-term sequels of Hemophilia: Permanent damage to knee and elbow joints.

- **Lab Diagnosis:**
  a. Bleeding time: N
  b. PT: N
  c. TT: N
  d. aPTT: prolonged; and corrected by mixing with normal plasma.
  e. Functional factor VIII coagulant activity is measured by one-stage clotting assays based on aPTT: low level of factor VIII but the Ag may be normal.

- **Treatment:**

  Factor VIII replacement therapy : infusion of factor VIII derived from human plasma OR recombinant FVIII (50–100 units/kg twice daily) to achieve FVIII levels of 1.0 unit/mL.



Hemophilia A:

PT : normal.

APTT : Prolonged.

TT : normal

F VIII : reduced.

HAEMOPHILIA B

- X linked recessive disease.
- Rarer than haemophilia A.
- *Incidence Ratio* is 1: 100000 male birth.
- Inheritance pattern and clinical features are similar to classical haemophilia.
- **Lab Diagnosis:**

  Assay of factor IX level which is lowered. Other lab findings are similar to haemophilia A.
- **Treatment:**

  recombinant FIX concentrate, Infusion of fresh frozen plasma or plasma enriched with factor IX.

VONWILLEBRAND'S DISEASE

- VonWillebrand's factor is **present** in both plasma and platelets and **acts as :**

  1. A carrier protein of Factor VIII.
  2. It is also plays an important role in platelets adhesion to subendothelium.

- The **VW Disease** represent a **most common** inherited coagulation disorder, due to deficiency of vonWillebrand's factor.
- This disorder is inherited mostly **as autosomal dominant**
- Disease classified to type 1 ,type 2 and type 3 according to the type of defect **quantitive or qualitative**

Table 38.4 Classification of von Willebrand disease.

Type	Description	Comments	Inheritance
1	Partial quantitative deficiency of VWF	Includes VWF mutations causing rapid VWF clearance (e.g. VWF Vicenza) and requires function:antigen ratio >0.6	Mostly autosomal dominant inheritance when VWF <0.3 IU/mL. Mutations of *VWF* in kindred with levels >0.3 IU/mL show variable penetrance
2	Qualitative VWF defects		
2A	Decreased VWF-dependent platelet adhesion with selective deficiency of high-molecular-weight multimers	Some controversy exists regarding classification of VWF mutations associated with subtle reductions in HMW multimers	Mostly autosomal dominant
2B	Increased affinity for platelet GPIb	Should be distinguished from platelet type pseudo-VWD (PT-VWD), using either platelet agglutination tests or genetic testing. Cases with normal VWF multimer and platelet count have been described	Autosomal dominant
2M	Decreased VWF-dependent platelet adhesion without selective deficiency of HMW multimers	This also includes defects of VWF collagen binding. May be combined quantitative/qualitative defect	Autosomal dominant
2N	Markedly decreased binding affinity for FVIII	Should be distinguished from mild haemophilia A	Reduced VWF:FVIII binding defects are more commonly identified in a compound heterozygote state with a VWF null allele rather than the classical homozygous form
3	Virtually complete deficiency of VWF	Equivalent to <0.03 iu/mL in most assays	Autosomal recessive, frequent null VWF alleles. Bleeding symptoms in 26-48% of obligate carriers

- **Clinically**
  - Mucous membrane bleeding, particularly epistaxis and menorrhagia.
  - Bruising and bleeding after trauma or during surgery are also common.
  - Haemarthrosis unlikely.

- **Lab Diagnosis:**
  - Prolonged bleeding time.
  - PT: normal
  - PTT: prolonged especially in type 2N & 3 but may be normal in mild cases.
  - Platelet count: normal except in type 2B & type 3(reduced).
  - Reduced plasma vWF concentration.
  - Defective platelet aggregation with ristocetin .
  - Reduced factor VIII activity.

- **Treatment:**

  Cryo-precipitates or Factor VIII concentrates

Acquired Coagulation Disorders

Vitamin K Deficiency

- **Vitamin K** serves as a cofactor in the formation of 6 prothrombin complex proteins (Vitamin K dependent coagulation factors) synthesized in the liver: Factor II, VII, IX, X, Protein C and Protein S.

- **Causes of Vitamin K deficiency:**
  - ✓Obstructive jaundice.
  - ✓Chronic diarrhoea.
  - ✓Liver disease.
  - ✓Haemorrhagic states in infants.

Lab Diagnosis:

Prolonged PT .

Treatment:

Parenteral administration of Vitamin K causes complete recovery in 48 hrs

Coagulation Disorder in Liver Disease

- Liver is the site of synthesis and metabolism of Coagulation Factors.

Factors promoting coagulation	Factors inhibiting coagulation
Synthesis of Coagulation Factors.	**Synthesis of Anti-thrombin 3, Protein C and Protein S**
Clearance of Fibrinolytic enzymes	**Clearance of Activated Factors**

- Liver disease leads to hypercoagulability and predispose to develop DIC and systemic fibrinolysis.

- **Liver disease** may be associated with **bleeding tendency** or may be with **hypercoagulability state** or may be both **as in DIC**
- **Lab Diagnosis:**

  Prolonged PT and a PTT, mild thrombocytopenia, decrease fibrinogen level and decreased hepatic stores of Vitamin k.

DISSEMINATED INTRAVASCULAR COAGULATION

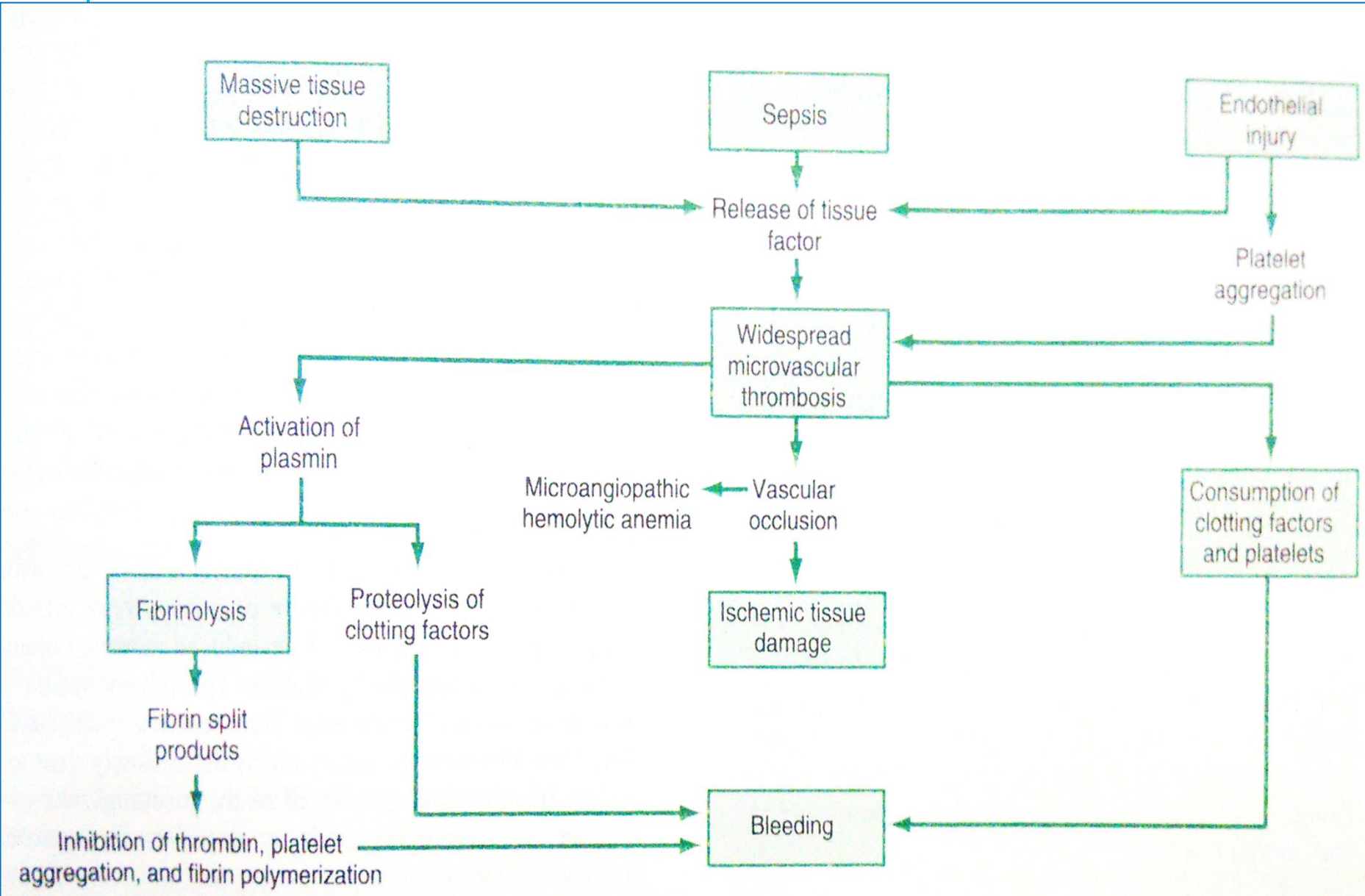
- Also called as defibrinate syndrome or consumption coagulopathy is a complex thrombo-haemorrhagic disease occurring as secondary complication of some systemic disease.

- *Major disorders associated with DIC:*
  - **Obstetrics Complications-** Abruption placentae, retained dead foetus, septic abortion, amniotic fluid embolism, toxaemia.
  - **Infections-** Gram negative sepsis, meningococcemia, rocky mountain spotted fever, malaria.
  - **Neoplasms-** Carcinoma of pancreas, prostate, lung and stomach.
  - **Massive Tissue Injury-** Traumatic, burns, extensive surgery.
  - **Miscellaneous-** Acute intravascular haemolysis, snake bite, giant haemangioma, shock, heat stroke.

- **Pathogenesis:**

  All the etiological factor act via 2 mechanisms-a. Release of tissue factor in the circulation. b. Widespread injury to endothelial cell.

Pathophysiology of Disseminated Intravascular Coagulation



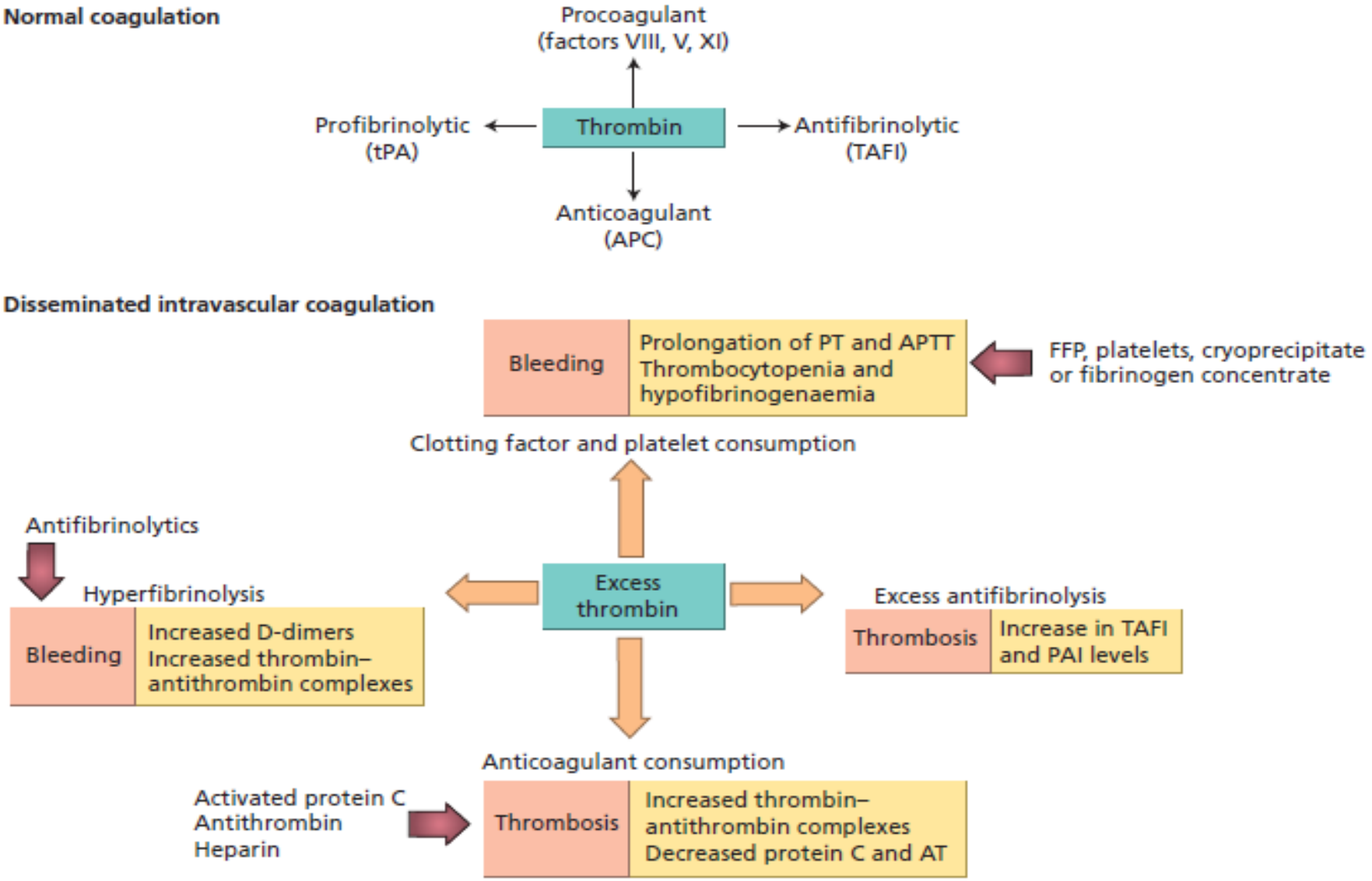


Figure 40.3 The changes in disseminated intravascular coagulation are compared with the normal coagulation. The excess thrombin generation in DIC leads to either bleeding or thrombosis (left) based on the predominant coagulation change (right) which has occurred. The therapeutic intervention in each setting is g by the arrow towards each double box. TAFI, thrombin activa fibrinolysis inhibitor; PAI, plasminogen activator; AT, antithrombin.

Clinical Features:

a. Widespread fibrin deposition within microcirculation leading to ischemia of organs like kidney and brain.

b. *Bleeding diathesis-* ensues as the platelets and clotting factors are consumed and there are secondary release of plasminogen activator but also digest Factor V and VIII there by reducing their concentration further.

Lab Diagnosis:

a. Reduced platelet count.

b. Blood film shows microangiopathic haemorrhagic haemolytic anaemia.

c. PT, TT,APTT are prolonged.

d. Plasma fibrinogen level is reduced.

e. Fibrin Degradation Products are raised.

Treatment:

Anticoagulants like heparin or coagulants contained in fresh frozen plasma, underlying disorder must be treated simultaneously.

THANK YOU

d!