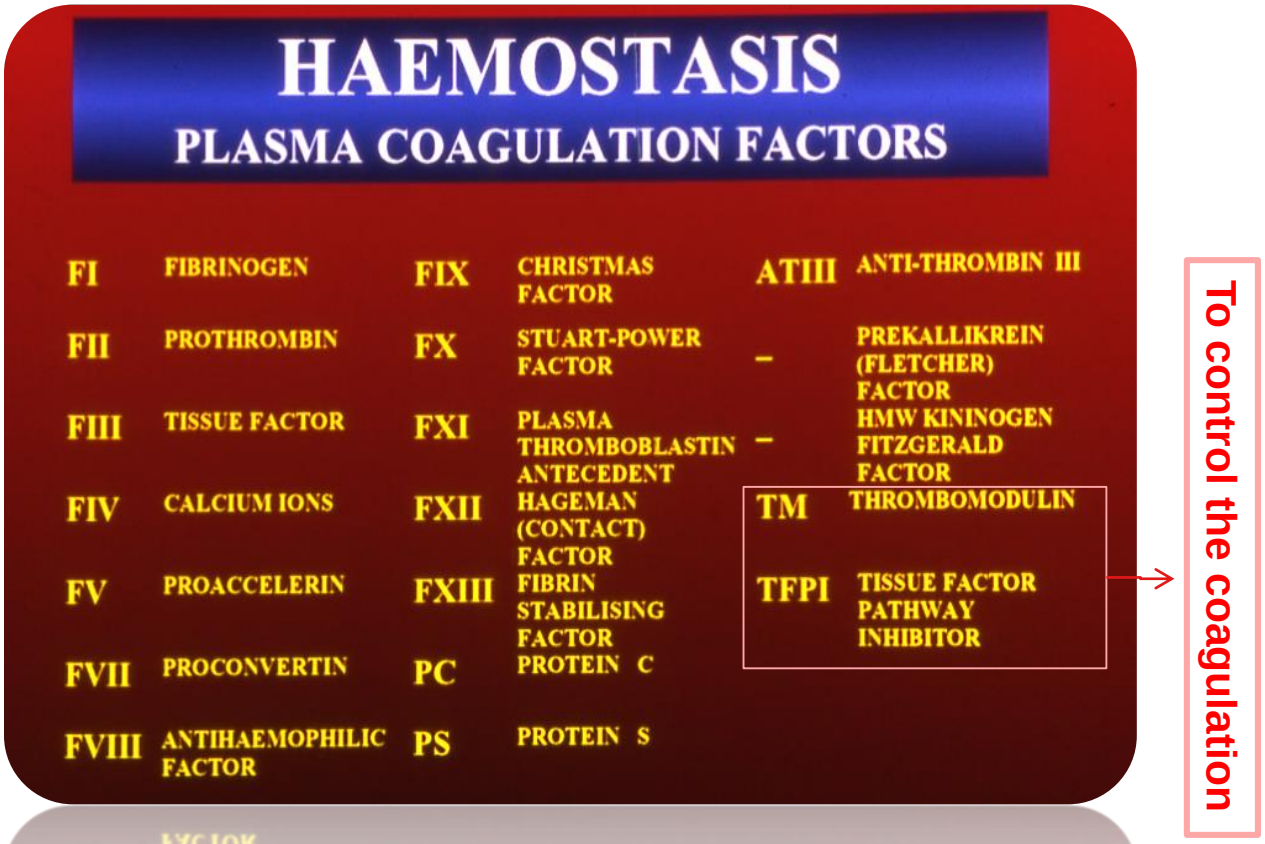
Lecture 12:
Bleeding Disorders

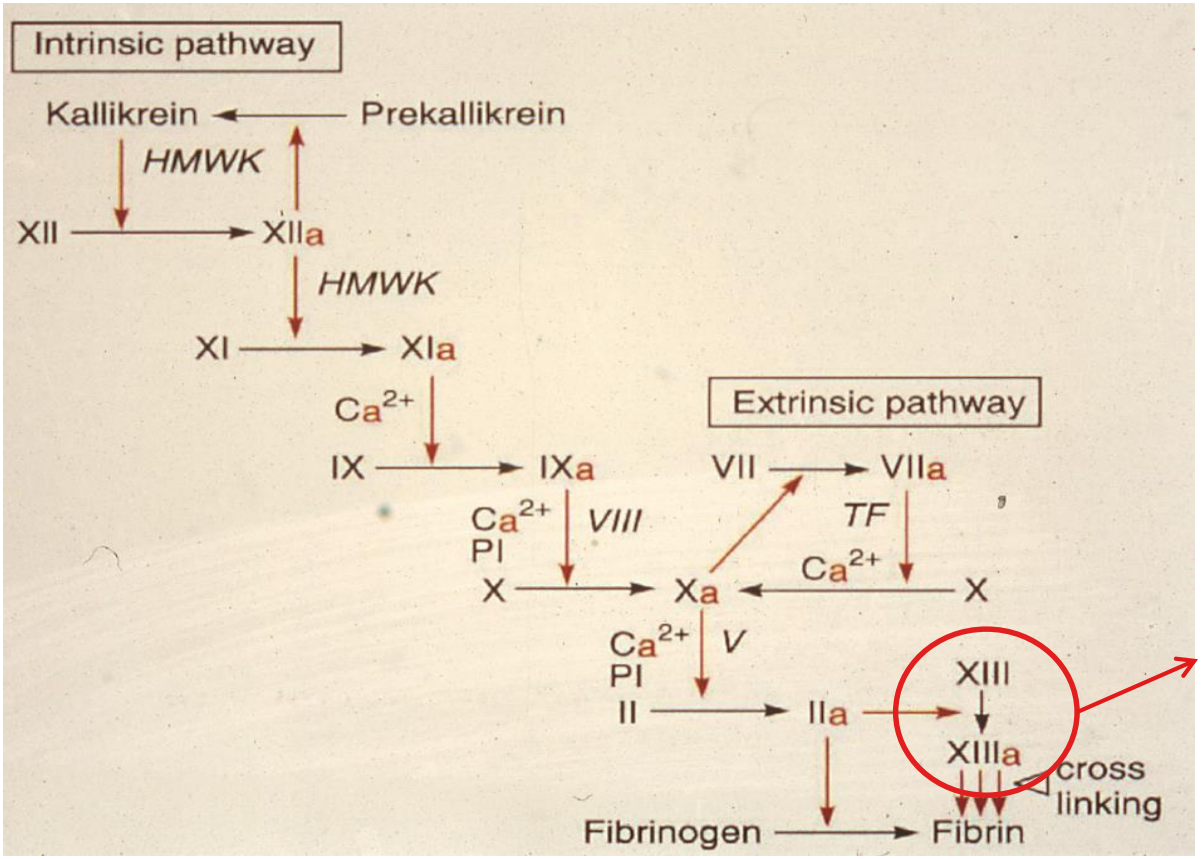
Hemophilia Presentation
Medical School - Coagulation Disorders
What is von Willebrand Disease?
What Is Hemophilia?

Normal constitutes needed for normal coagulation process and to avoid bleeding:

- Normal platelet
- Normal Blood Vessels
- Normal coagulation Factors : they are found in the circulation in inactive form. And they are activated as soon as injury occurs.



Mechanism of coagulation

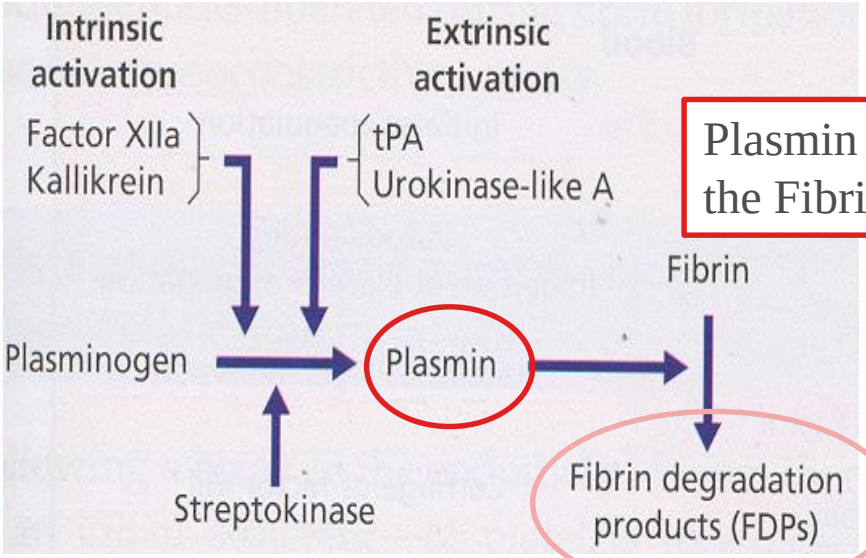


More details in physiology lecture

Factor XIII is mainly for stabilizing the fibrin

- 2 pathways are involved in the coagulation process (intrinsic and extrinsic).
- Extrinsic pathway : starts by the release of Tissue Factor from the injured area (TF)* which will convert Factor VII to the active form VIIa this will convert Factor X to the active form too Xa.
- Intrinsic pathway will lead at the end to the same result of the extrinsic one which is activation of factor X.
- The two pathways will meat at the COMMON FINAL PATHWAY (from the step of factor X to Fibrin formation)

*TF : is the main stimulus for coagulation cascade.



Plasmin Function is to breakdown the Fibrin (Fibrinolysis)

Main cause of DIC (Disseminated intravascular hemorrhage)

- Inherited coagulation disorders

I. HAEMOPHILIA:

- **A due to Factor VIII Deficiency**
- **B due to Factor IX Deficiency (Christmas Disease)**
- **C due to Factor XI Deficiency**

Note : Haemophilia A & B are similar in everything except the affected factor.

II. Von Willebrand Disease*

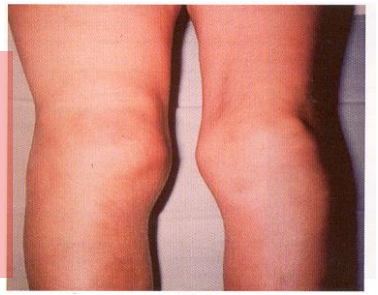
*Note: **Von Willebrand Factor (vWF) is important for 2 reasons: (platelet-collagen adhesion and carrier for factor VIII)**

Correlation of coagulation factor activity and disease severity in haemophilia A or hemophilia B

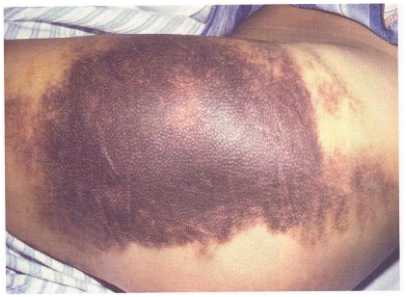
Coagulation factor activity	Clinical manifestations (Severity)
<1 % (Less than 1%)	***Severe disease** ***Frequent spontaneous bleeding episodes** ***Joint deformity and crippling** (if not adequately treated)
1 – 5 %	***Moderate disease** ***Post-traumatic bleeding** ***occasional spontaneous episodes**
5 – 20 %	***Mild disease** ***Post-traumatic bleeding**

CLINICAL FEATURES OF HAEMOPHILIA :

May lead to progressive deformities that can be crippling.

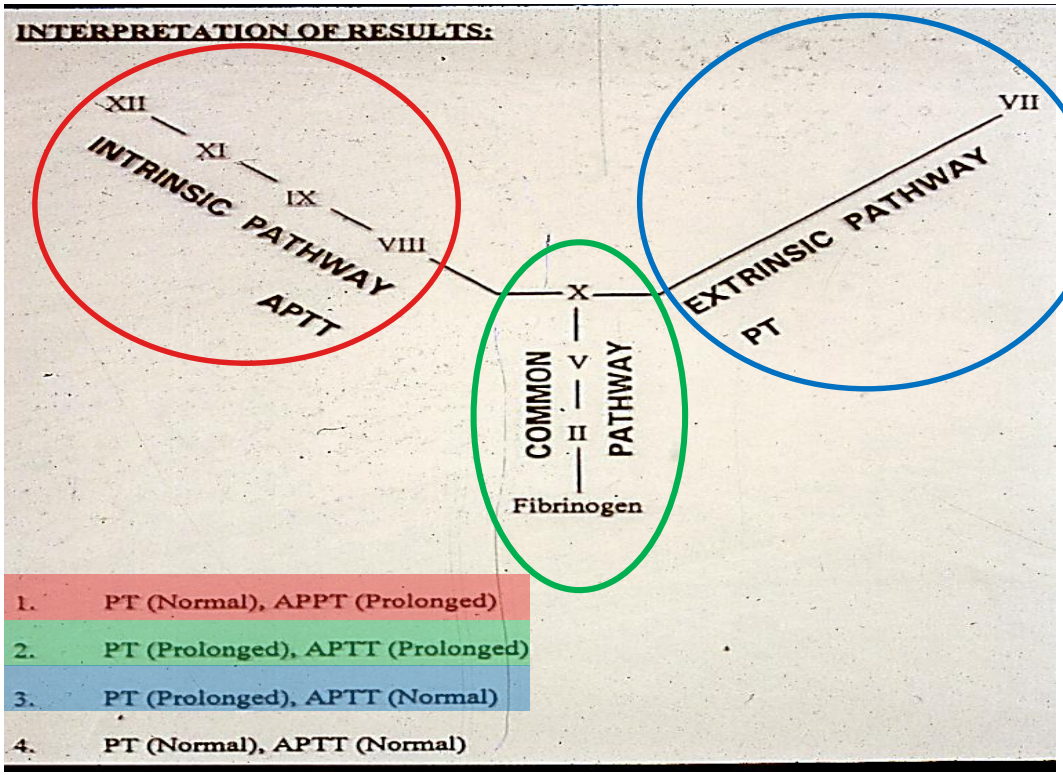


Hemarthoses (joint bleeding)



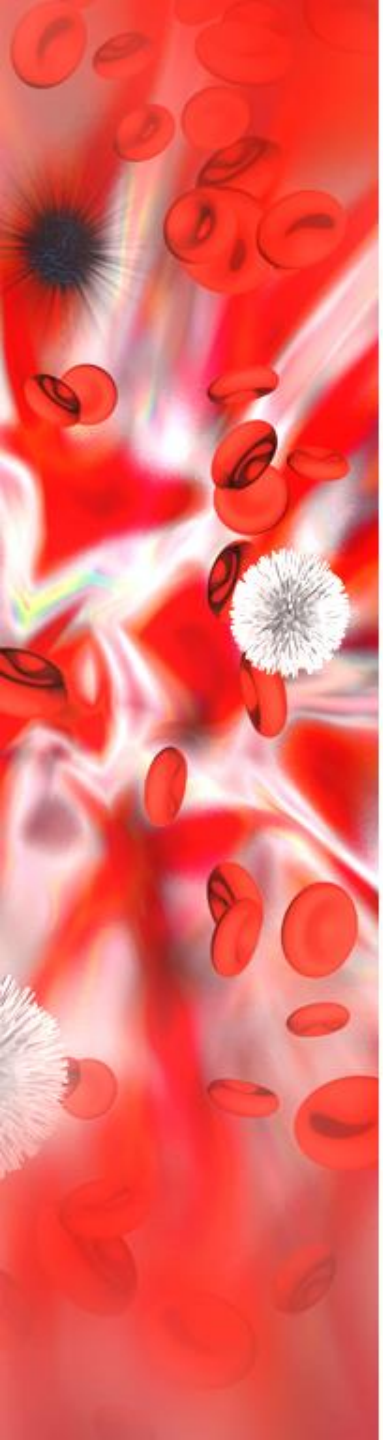
Muscle bleeding

How to diagnose the disease ?



IMPORTANT

Special tests need to be done to differentiate if the patient has a problem in which pathway and then we will be able to know which factor is affected.
These tests include measurement of PT (prothrombin time) and APTT (activated partial thromboplastin time).
As shown in the picture :
#1. indicates a problem in intrinsic pathway “Factors XII, XI, IX, VIII” (because APTT is prolonged)
#2. indicates a problem in the common Pathway (because both PT and APTT are prolonged)
#3. indicates a problem in extrinsic pathway “Factor VII” (because PT is prolonged)



How to differentiate between Haemophilia A&B and VW disease?

Haemophilia A & B are similar except in the affected factor. But VW disease has totally different characteristics.

	Haemophilia A or B	VW disease
Inheritance	Sex-linked	Dominant
Site of hemorrhage	Muscle - joints	Mucous membranes – skin cuts
Bleeding time	Normal	Prolonged (because vW factor has a role in the aggregation)
PT	Normal	Normal
PTT	Prolonged	Prolonged or normal
Affected factor	A: factor VIII , B: factor IX	Factor VIII (because VW is carrier for factor VIII)
VW factor	Normal	Decreased or has abnormal function
Platelet aggregation test	Normal	Abnormal

Classification of VW disease :

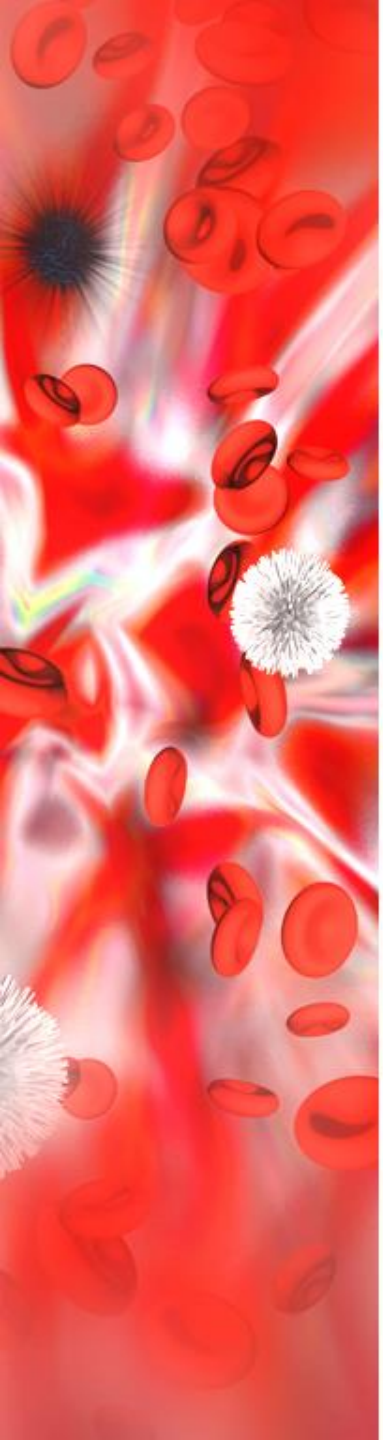
Important

Type 1: Partial quantitative vWF deficiency.

Type 2: Qualitative deficiency(Functional abnormality) *Has many sub classification

Type 3: Complete vWF deficiency.

Note: Platelet count is normal in all these diseases.



Treatment of VW disease and Haemophilia A&B*:

*Doctor said it's not important

1.Replacement therapy :

- Cryoprecipitate (Antihaemophilic Factor)
- Factor VIII concentrate. (the level of factor VIII after the first transfusion depends on the signs and symptoms :

Signs and symptoms	The wanted Level of VIII to be rised
Early haemarthoses – external bleeding	20-30%
Dental extraction – severe haemarthoses Internal hemorrage	50-10%
Major surgery – serious accedint	70-100 %

- Factor IX concentrate (for type B)
- Fresh frozen plasma (for other factor deficiency)
- DDAVP (vasopressin – in mild haemophilia A and VW disease) *used sometimes as nasal spray = cause slight increase in factor VIII *

2.Surgical orthopedic treatment (joint replacement)

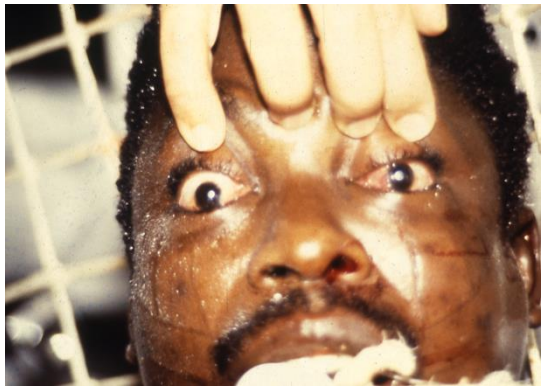
3.Prophylactic treatment (early before the complication development) *factor VIII or IX three times/week*

4.Treatment for patient with inhibitors (5-10% of haemophilia patients develop antibodies against the replacement therapy. These antibodies known as "inhibitors". To treat them we should do the following :

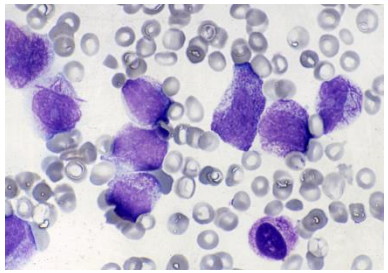
#High dose of factor VIII. #Recombinant activated factor VII
#immunosuppression (cyclophosphamide) #intravenous immunoglobulin.

- Disseminated intravascular coagulation (DIC)*

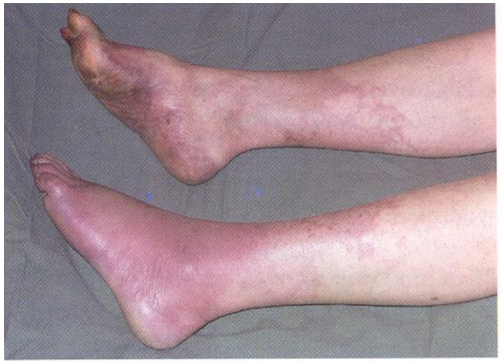
When a foreign substance reach to the circulation it will cause endothelial damage then it will lead to generalized platelet aggregation (response to stimulus) and then it will activate the coagulation cascade leading to microthrombie in the circulation which will cause blocking for many areas. (may lead to gangrene due to the blocking). Later on, the platelet and coagulation factors are consumed and fibrinolysis is activated leading to bleeding related to pathologic activation of fibrinolysis and the depletion of the elements needed for hemostasis.



Severe bleeding due to fibrinolysis activation

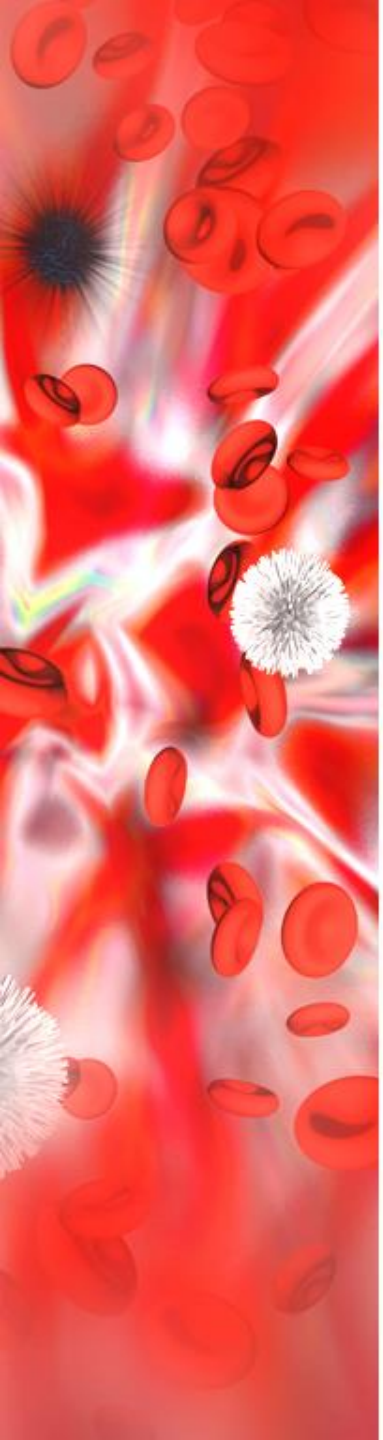


Blast (Acute promyelocytic leukemia)



Blocked circulation in the lower limb due to thrombie

*Other names :
Consumption coagulationpathy.
Defibrination syndrome



DIC (Cont..)

Causes :

- infection

Gram-negative and meningococcal septicemia
Clostridium
Falciparum malaria
Viral infection – varicella, HIV, hepatitis, cytomegalovirus.

- Malignancy

mucin-secreting adenocarcinoma
Acute promyelocytic leukaemia **(AML-M3)**.

- Obstetric complications

Amniotic fluid embolism
Premature separation of placenta
Septic abortion

- Hypersensitivity reactions

Anaphylaxis (Drug induced)
Incompatible blood transfusion

- Widespread tissue damage

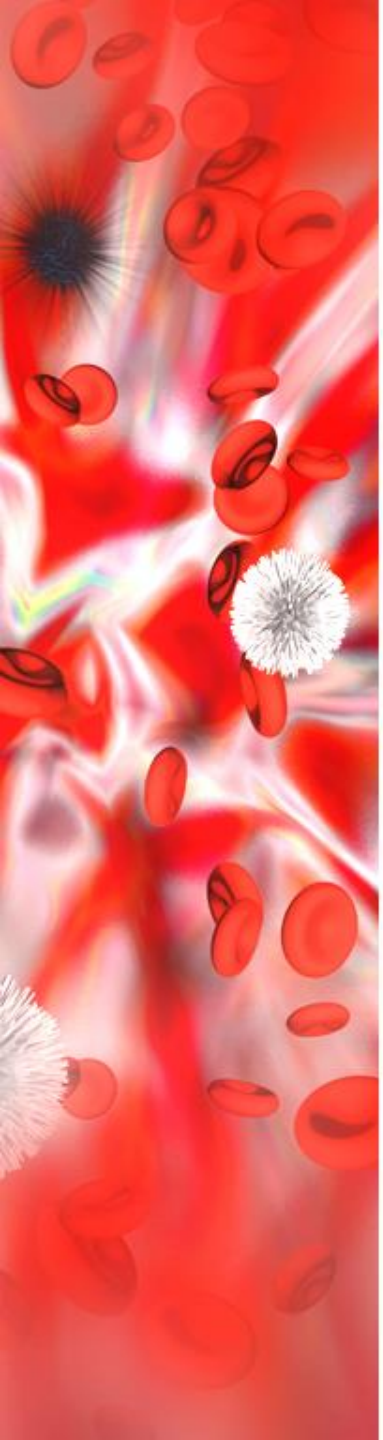
Following surgery or trauma
After severe burns

- Vascular abnormalities
- Snake and invertebrate venoms
- Acute hypoxia

Needed tests :

1.PT normally 10-14s. and APTT normally 30-40s.
2.Thrombin time (TT). Normally 10-12s
3.Plasma fibrinogen
4.Coagulation factor assay
5.Plasma fibrin / Fibrinogen degradation product (FDP's) and D-dimers.
6.Platelet count.

In case of DIC the patient will have (low platelet count , prolonged PT, APPT and TT and high FDP's)



Summary from Essential Hematology for Coagulation disorders

- Coagulation disorders may be inherited or acquired.
- Haemophilia A is the most common inherited deficiency of a clotting factor. It is severe if factor VIII activity in plasma is <1% of normal. It presents with excess bruising or prolonged bleeding after trauma and spontaneous bleeding, usually into muscles and joints, which can result in joint deformity.
- Many older patients are infected with hepatitis C or HIV as a result of receiving contaminated blood products.
- The APTT is prolonged and PT normal.
- Antenatal diagnosis is usually carried out by polymerase chain reaction (PCR) techniques, the gene being carried on the X chromosome.
- Treatment is with recombinant or concentrates of factor VIII, or with drugs (e.g. DDAVP (desmopressin)).
- Factor IX deficiency has a similar pattern of inheritance and clinical manifestations.
- Von Willebrand disease (VWD) is the most frequent inherited bleeding disorder. Haemorrhage occurs from mucous membranes, skin cuts and post-trauma. It usually has a dominant inheritance. Platelet function is abnormal and VWF levels usually low.
- Acquired coagulation disorders include those caused by vitamin K deficiency (e.g. in the newborn or with malabsorption) or caused by vitamin K antagonist therapy (e.g. warfarin).
- Other common coagulation abnormalities are those in liver disease caused by reduced synthesis of coagulation factors and in disseminated intravascular coagulation (DIC), which causes consumption of coagulation factors and platelets.
- Fresh frozen plasma is used in treatment of multiple coagulation defects, or specific defects if the appropriate concentrate is not available, and in therapy for thrombotic thrombocytopenic purpura.

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