Bleeding Diathesis: Inherited coagulation disorders

- Normal hemostatic system
  - vessel wall
  - circulating blood platelets
  - blood coagulation and fibrynolysis
- **inherited** or acquired defects of
  - vessel wall
  - platelets number and/or function
  - **coagulation system**
- Bleeding diathesis characterised by
  - spontaneous bleeding
  - extensive bleeding after minimal trauma

The hemophilias A and B

- X-linked hereditary blood clotting disorders due to:
  - Deficiency of factor VIII (hemophilia A)
  - Deficiency of factor IX (hemophilia B)

- Identical clinical manifestations, screening tests abnormalities and sex-linked genetic transmission

Epidemiology

The incidence rate:

- Hemophilia A
  - 1 per 5000 live male births
- Hemophilia B
  - 1 per 25 000- 30 000 live male births
- Found in all ethnic groups, in all parts of the world

Etiology and pathogenesis (1)

Hemophilias result from defects in the factor VIII/IX gene that leads to:

- decreased amount of f. VIII/IX protein
- the presence of a functionally abnormal protein
- or combination of both

Inheritance patterns for hemophilia A and B

		Hemophilic male X^hY	
Normal female	X	XX^h Carrier female	XY Normal male
	X	XX^h Carier female	XY Normal male

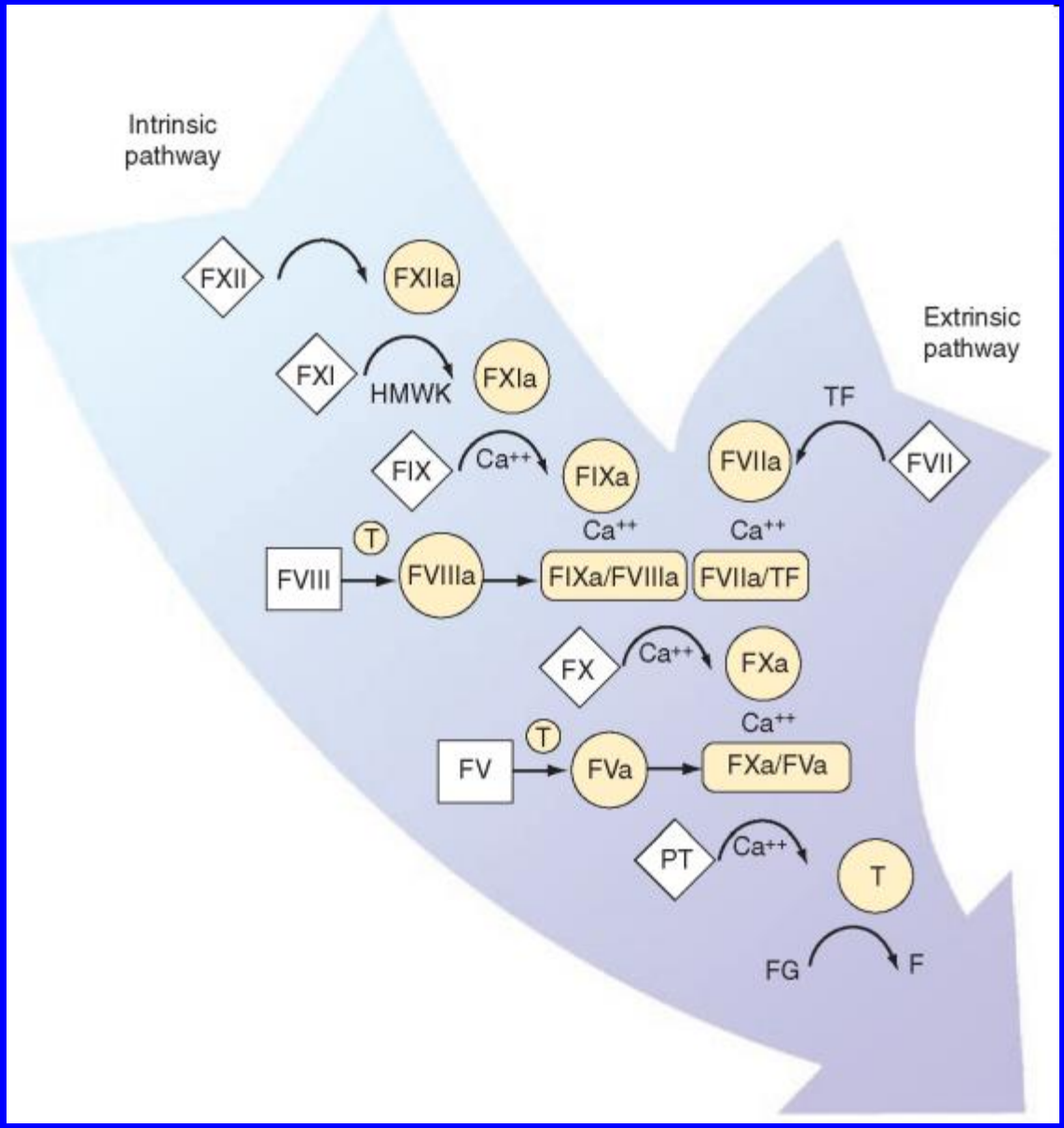
Inheritance patterns for hemophilia A and B

		Normal male XY
Carrier female	X^h	XX^h Carrier female
	X	XX Normal female

		X^h Y Hemophilic male
		XY Normal male

Queen Victoria
(24 May 1819 – 22 January 1901)

Prince Leopold, Duke of Albany
(7 April 1853 – 28 March 1884)


Intrinsic pathway
Extrinsic pathway
FXII
FXIIa
FXI
HMWK
FXIa
TF
FIX
Ca++
FIXa
FVIIa
FVII
Ca++
Ca++
T
FVIII
FVIIIa
FIXa/FVIIIa
FVIIa/TF
FX
Ca++
FXa
Ca++
T
FV
FVa
FXa/FVa
PT
Ca++
T
FG
F

Clinical features

- Excessive bleeding into various parts of the body
  - hemarthroses
  - hematomas
  - hematuria
  - hemorrhage into the central nervous system
  - mucous membrane hemorrhage
  - pseudotumors (blood cysts)
  - dental and surgical bleeding

Hemarthroses

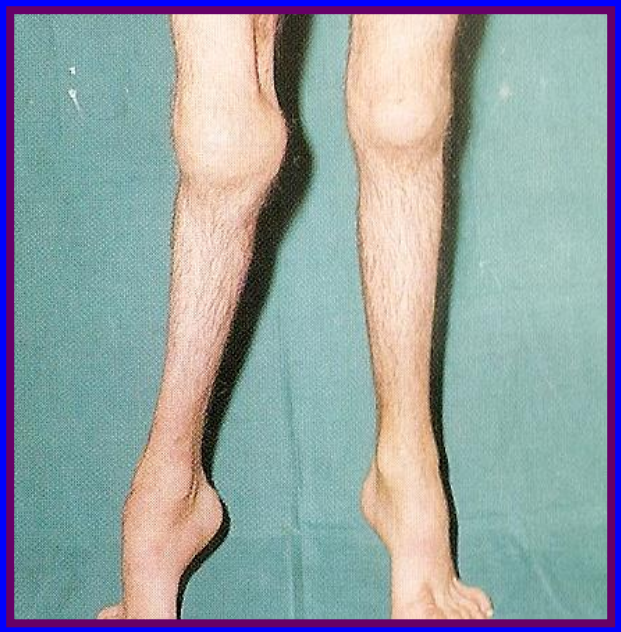
- Bleeding into joints accounts for about 75% of bleeding episodes in severely affected patients

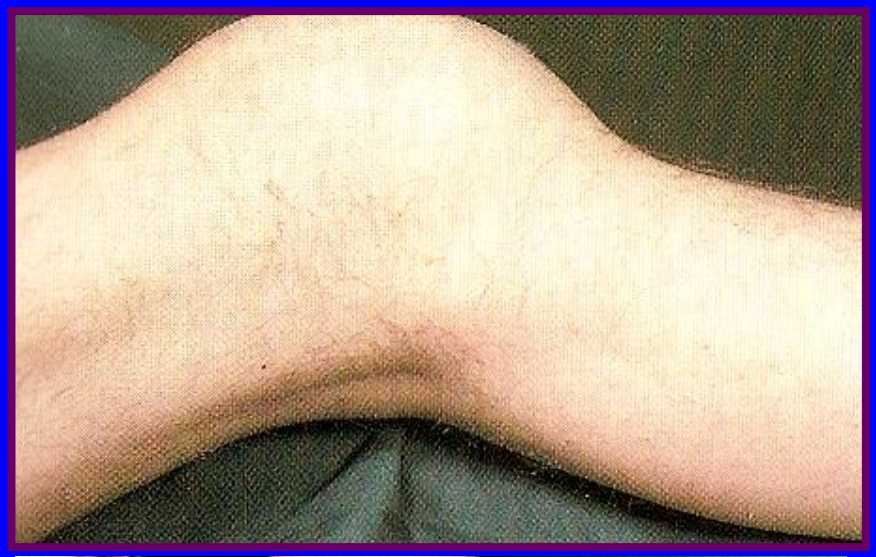
- The joints most frequently involved:
  - knees, elbows, ankles, shoulders , wrists and hips

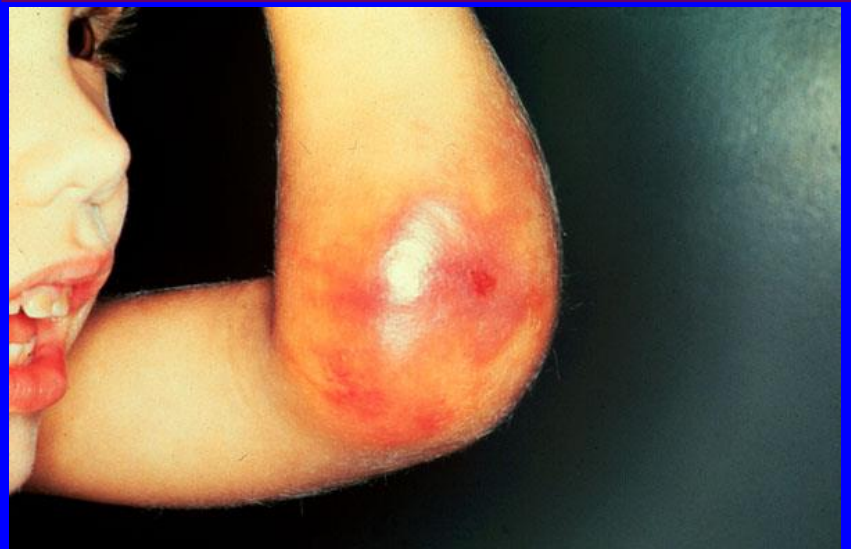
- Repeated hemarthroses
  - destruction of articular cartilage, synovial hypertrophy and inflammation

- The major complication of repeated bleeding is joint deformity complicated by muscle atrophy and soft tissue contractures (hemopilic artropathy)

Hemopilic artropathy

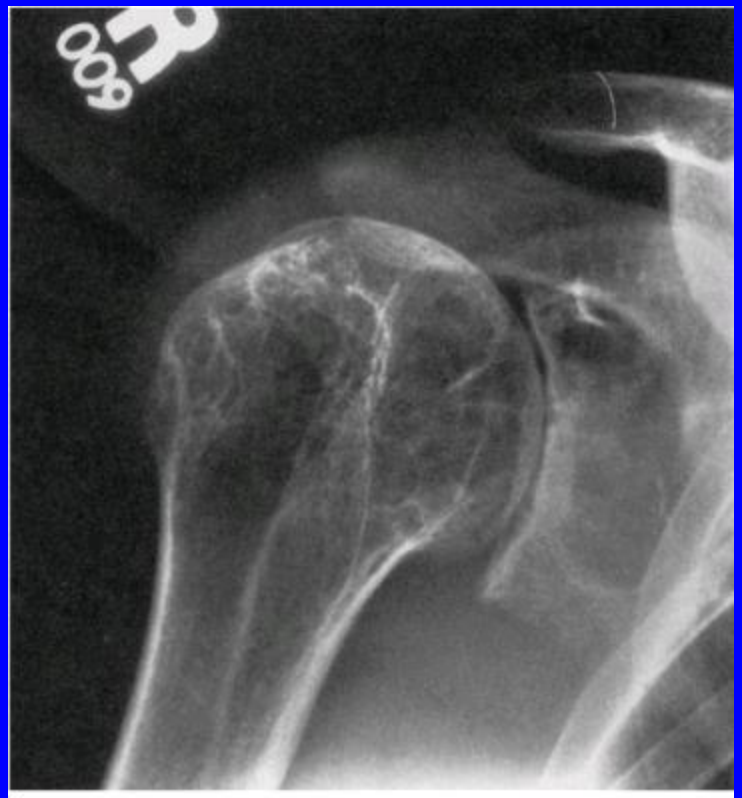






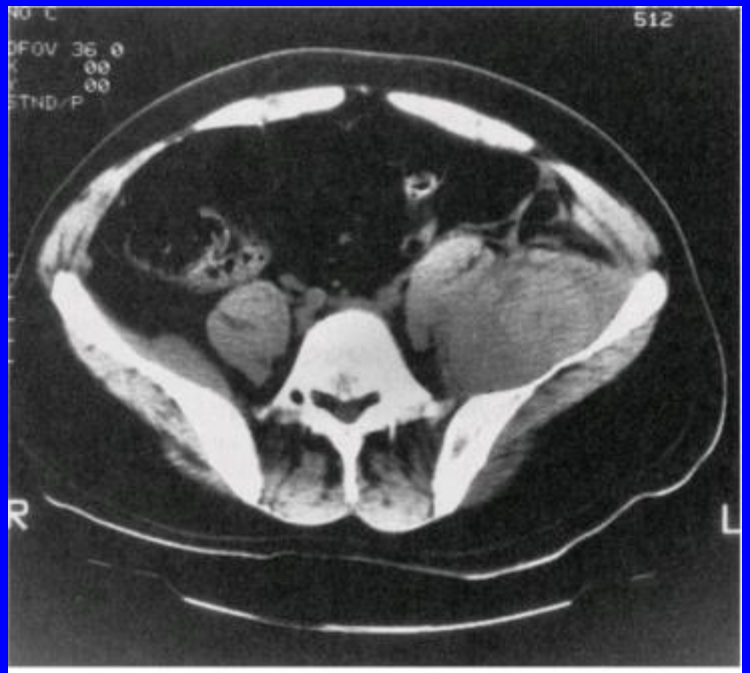
Neurologic complications

- **Hemorrhage into the central nervous system**
  - the most dangerous event in hemophilic patients
  - Intracranial bleeding may be spontaneous or follows trauma, which may be trivial
  - Hemophilic patients with unusual headaches should always be suspected of having intracranial hemorrhage
- **Hemorrhage into the spinal canal**
  - can result in paraplegia
- **Peripheral nerve compression**
  - a frequent complication of muscle hematomas, particularly in the extremities



A

Multiple subchondral cysts in the head of the humerus are an early finding in hemophilic arthropathy, seen in this radiograph of the shoulder. The glenohumeral joint space is still fairly well preserved, and the range of motion is normal.



Retroperitoneal hemorrhage involving the iliopsoas muscle of the left iliac fossa in a patient with hemophilia A

Clinical classification of hemophilia

Classification	Factor VIII/IX level	Clinical features
Severe	0-1% of normal	1. Spontaneous hemorrhage from early infancy 2. Frequent spontaneous hemarthroses and other hemorrhages
Moderate	1-5% of normal	1. Hemorrhage secondary to trauma or surgery 2. Occasional spontaneous
Mild	6-30% of normal	1. Hemorrhage secondary to trauma or surgery 2. Rare spontaneous hemorrhage

Factor VIII/IX activity- definition

- 1 unit of factor VIII/IX:
  - equal to the amount in 1ml of pooled fresh normal human plasma

- 1 unit of factor VIII/IX/ml =
  100% of normal activity

Laboratory features

- Prolonged activated partial thromboplastin time (aPTT)
  - the aPTT is corrected when hemophilic plasma is mixed with an equal volume of normal plasma
- Normal prothrombin time, thrombin-clotting time, bleeding time
- A definitive diagnosis of hemophilia A/B should be based on specific assay for factor VIII/IX coagulant activity

Therapy- general principles

- Avoidance of aspirin, non-steroid anti-inflammatory drugs and other agents interfering with platelet aggregation
- Addictive narcotic agents should be used with great caution
- Avoidance of intramuscular injections

Factor VIII replacement therapy

Factor VIII concentrates:

- plasma-derived
  - intermediate purity, high purity and ultrapure concentrates after viral inactivation by pasteurization or by exposure to solvent detergent
- produced by recombinant DNA technics

Factor VIII replacement therapy

- The site and severity of hemorrhage determine the frequency and dose of factor VIII to be infused

- The dose of factor VIII calculation for practical purpose:
  - 1 unit of factor VIII/kg will raise the circulating f. VIII level about 2% (0.02 U/ml)
  - after the initial dose of f. VIII further doses are based on a half- life of 8 to 12 h

Doses of factor VIII for treatment of hemorrhage

Site	Desired f. VIII level %	F.VIII Dose Unit/kg	Frequency q hours	Duration, days
Hemarthroses	30-50%	~25	12-24	1-2
Superficial intramuscular hematoma	30-50%	~25	12-24	1-2
Gastrointestinal tract	~50 %	~25	12	Until resolved
Epistaxis	30-50%	~25	12	Until resolved
Hematuria	30-100%	~25-50	12	Until resolved
Central nervous system	50-100%	~50	12	At least 7-10 days
Retropharyngeal, retroperitoneal	50-100%	~50	12	At least 7-10 days

DDAVP in the treatment of hemophilia A

- DDAVP (1,8-desamino-D-arginine vasopressin, desmopressin) causes a transient rise in factor VIII in normal subjects and in patients with mild to moderate hemophilia A
- After a dose 0.3 μg per kg i.v or s.c. F. VIII level increases two- to threefold above baseline
- Repeated administration of DDAVP results in a diminished response (tachyphylaxis)

Factor VIII prophylactic therapy

- It should be considered in all severely affected patients
- The administration of 25-40 U factor VIII/kg three times weekly markedly decreases the frequency of hemophilic arthropathy and other long-term effects of hemorrhages episodes

Factor IX replacement therapy

Factor IX concentrates:

- plasma-derived
  - intermediate purity- prothrombin complex concentrates
  - high purity
- produced by recombinant DNA technics
- viral inactivation: dry heat 80^{o}C, pasteurization, solvent detergent

Factor IX replacement therapy

- The dose of factor IX calculation for practical purpose:

- 1 unit of factor IX/kg will raise the circulating f. IX level about 1% (0.01 U/ml)
  - intravascular recovery of factor IX is about 50% (probably f. IX binds to collagen type IV of the vessel wall)

- the initial dose of f.IX should be followed by one-half this amount every 12 to 18 h

Antifibrynolytic agents

- Fibrynolytic inhibitors (epsilon-aminocapric acid EACA, tranexamic acid) may be given as adjunctive therapy for bleeding from mucous membranes, particularly for dental procedure

- Doses: tranexamic acid (Exacyl) 1g every 6 h

  EACA 4 g every 6 h

von Willebrand disease

- the most common inherited bleeding disorder in humans
- quantitative or qualitative abnormalities in von Willebrand factor (vWF)
- von Willebrand factor
  - a central component of hemostasis, secreted by endothelial cells, that circulates in plasma in multimers, serving both as a carrier for factor VIII and as an adhesive link between platelets and the injured blood vessel wall

von Willebrand disease- epidemiology

- The overall prevalence of von Willebrand disease is 1% of the general population
- The prevalence of clinically significant disease is closer to 1: 1000

Classification of von Willebrand disease

- **Type 1 vWD- the most common variant**
  - autosomal dominant in inheritance
  - normal vWF in structure and function but decrease in quantity- range 25-50% of normal
- **Type 2 vWD (2A, 2B, 2M, 2N)**
  - autosomal dominant in inheritance
  - vWF is abnormal in structure and/or function
- **Type 3 vWD**
  - autosomal recessive in inheritance
  - the most severe form characterized by very low or undetectable level of vWF

Clinical symptoms

- Mucocutaneous bleeding- the most common symptom
  - epistaxis
  - easy bruising and hematomas
  - menorrhagia
  - gingival bleeding
  - gastrointestinal bleeding
- spontaneous hemarthroses occur almost exclusively in patients with type 3 vWD

Laboratory features

- Screening tests:
  - bleeding time- normal or prolonged
  - aPTT- prolonged or normal
  - PT- normal

- The routine tests:
  - activity of factor VIII- decreased
  - vWF antigen- decreased
  - ristocetin cofactor activity assay- decreased agglutination of platelets in the presence of ristocetin
  - analysis of plasma vWF multimers- critical for subclassification of vWD

Therapy

- **Desmopressin**
  - a dose 0.3 μg per kg i.v or s.c., upper limit 20 μg , repeated 3 or 4 times every 24 hours
  - the best results in type 1 vWD- effective in 80% patients
  - many patients with type 2 and nearly all ones with type 3 do not respond to DDAVP
- **vWF replacement therapy**
  - vWF-containing factor VIII concentrates: Humate P, Koate HP

Nonreplacement therapy

- Estrogen or oral contraceptives in treating menorrhagia
- fibrynolytic inhibitors

The other uncommon inherited deficiencies of coagulation factors

- Bleeding tendencies caused by inherited deficiency of:
  - factors I, II, V, VII, X, XI and XIII
  - rare disorders, distributed worldwide

- Treatment may be necessary during spontaneous bleeding episodes, during or after surgical procedures

- In most deficiency states fresh frozen plasma replacement is used, but specific concentrates of factors I, II, VII, X, XI and XIII are also available