همایش تازه های تشخیص و درمان بیماری های شایع

# Coagulation Disorder Diagnosis and Treatment

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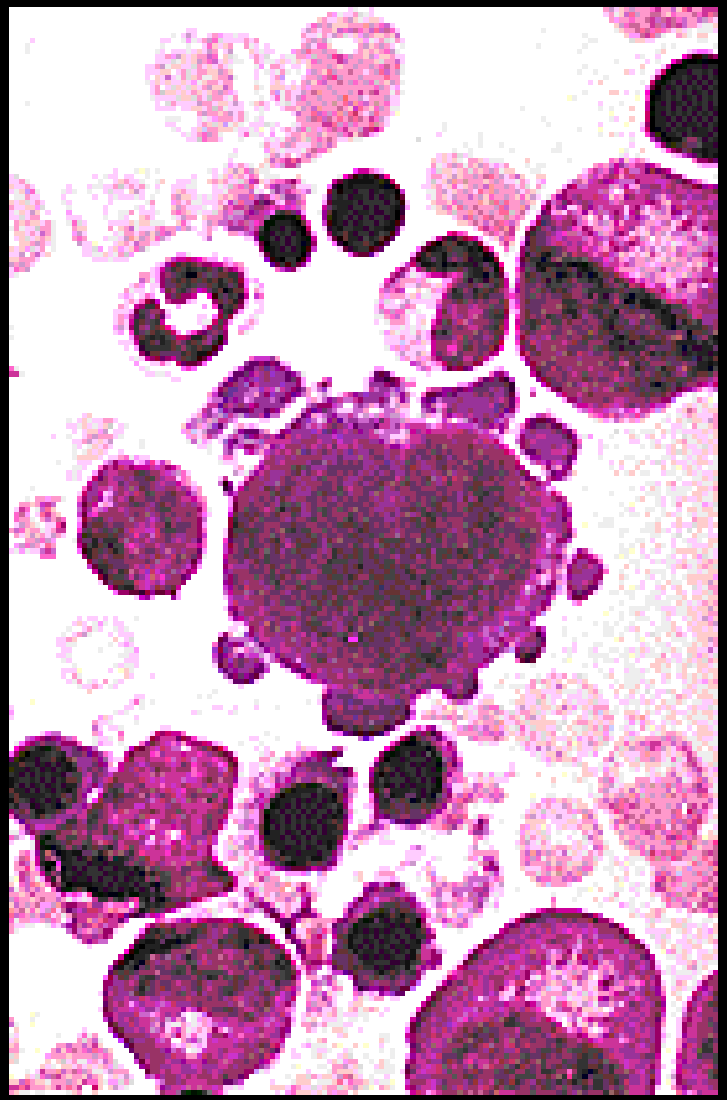
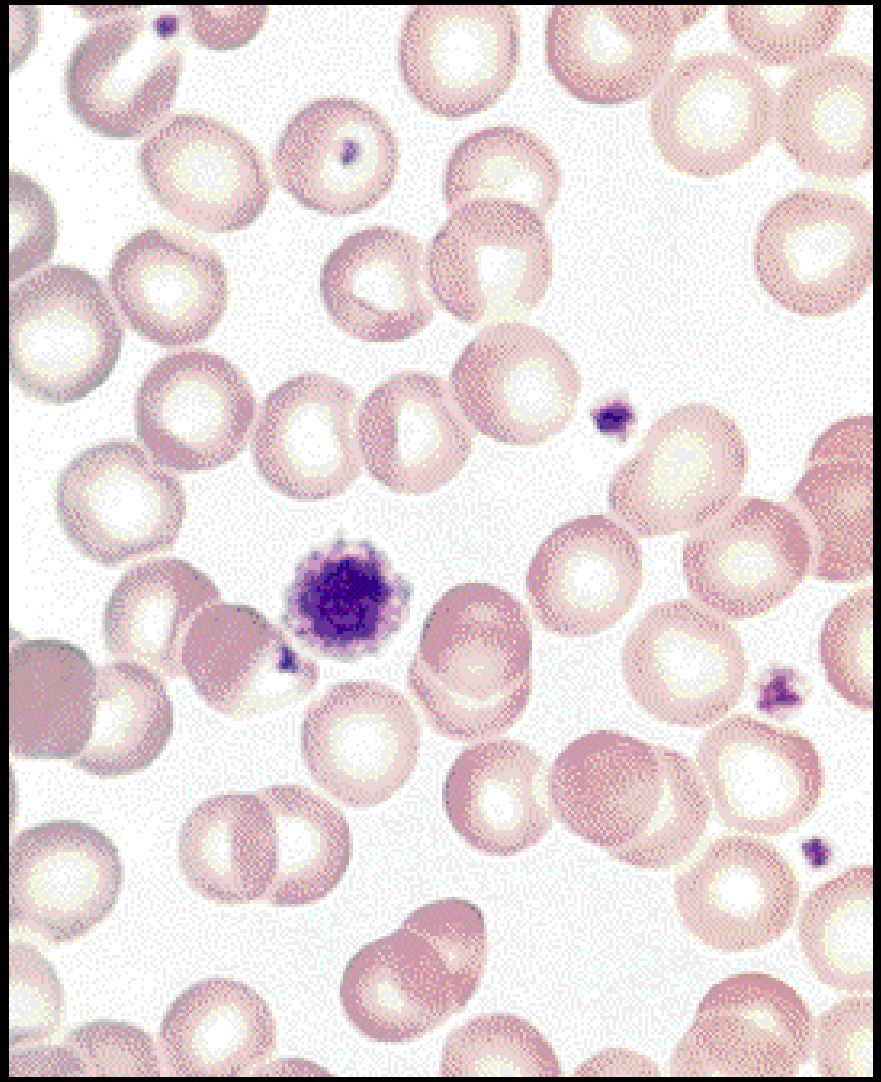
# Introduction

- An efficient and rapid mechanism for stopping bleeding from sits of blood vessel injury is clearly essential for survival. Homeostasis is the process of blood clot formation at the site of vessel injury. Abnormal bleeding or a propensity to no physiologic thrombosis (ie, thrombosis not required for haemostatic regulation) may occur when specific elements of these processes are missing or dysfunctional.

- The five major components involved are platelets, coagulation factors, coagulation inhibitors, fibrinolysis and blood vessels.

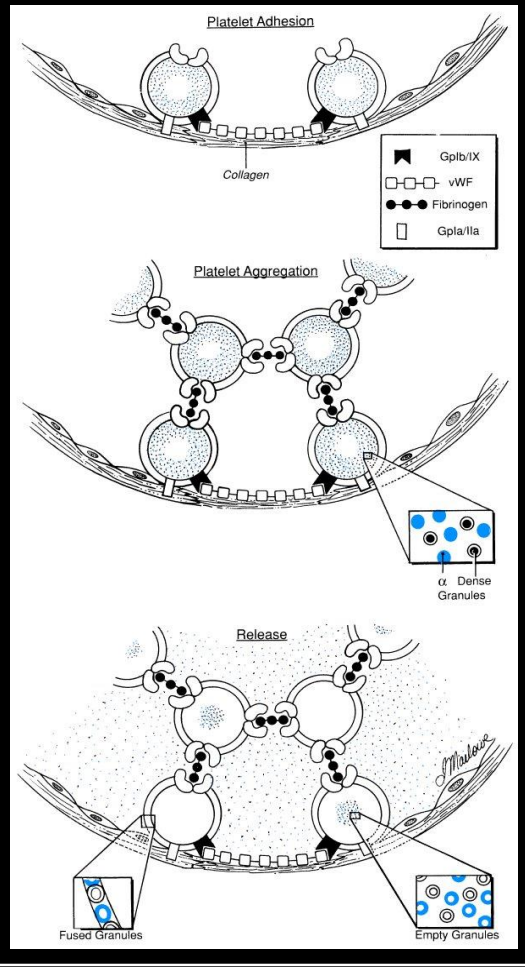




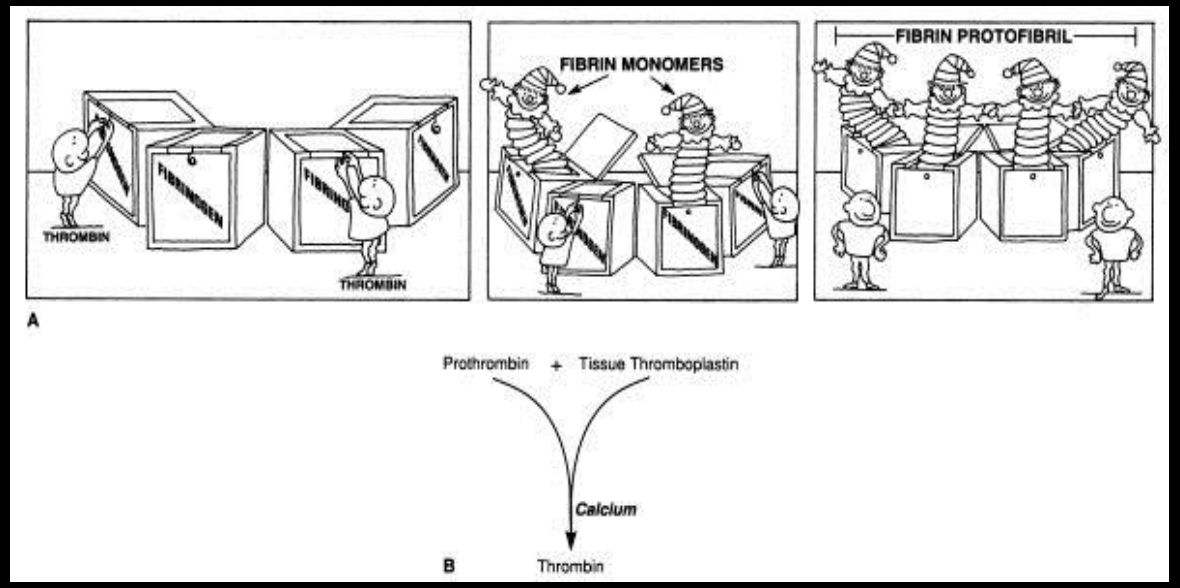
# Platelet function

The functional response of activated platelets involves four different processes:

- Adhesion : The deposition of platelets on the subendothelial matrix.
- Aggregation :Platelet-platelet cohesion.
- Secretion :The release of platelet granule proteins.
- Procoagulant activity :The enhancement of thrombin generation.



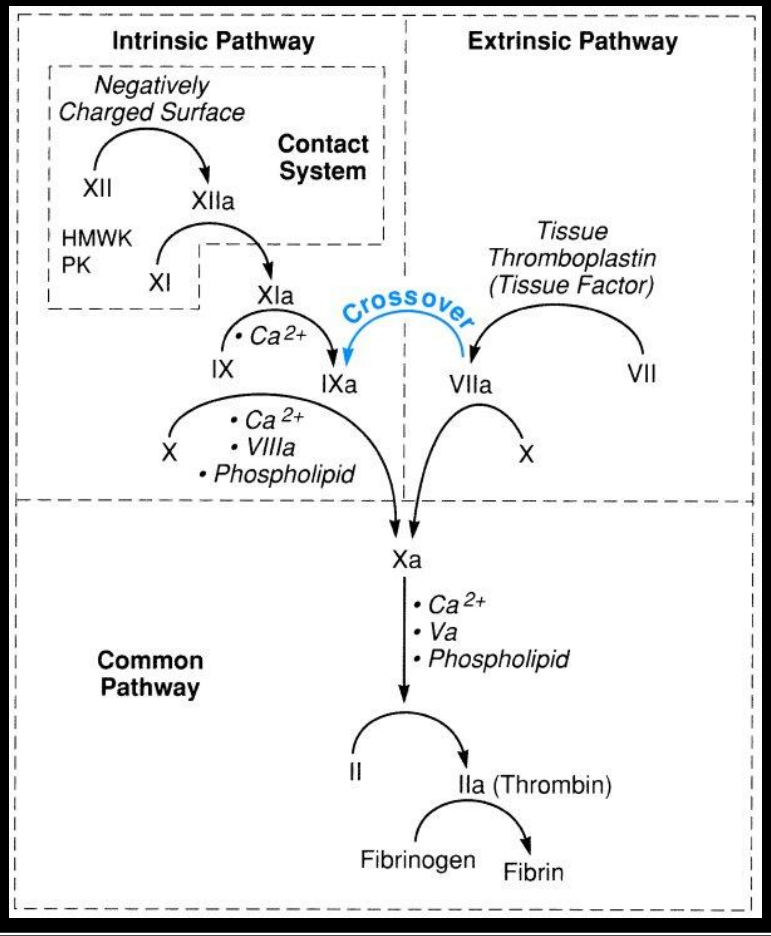
# CLOTTING CASCADE AND PROPAGATION OF THE CLOT



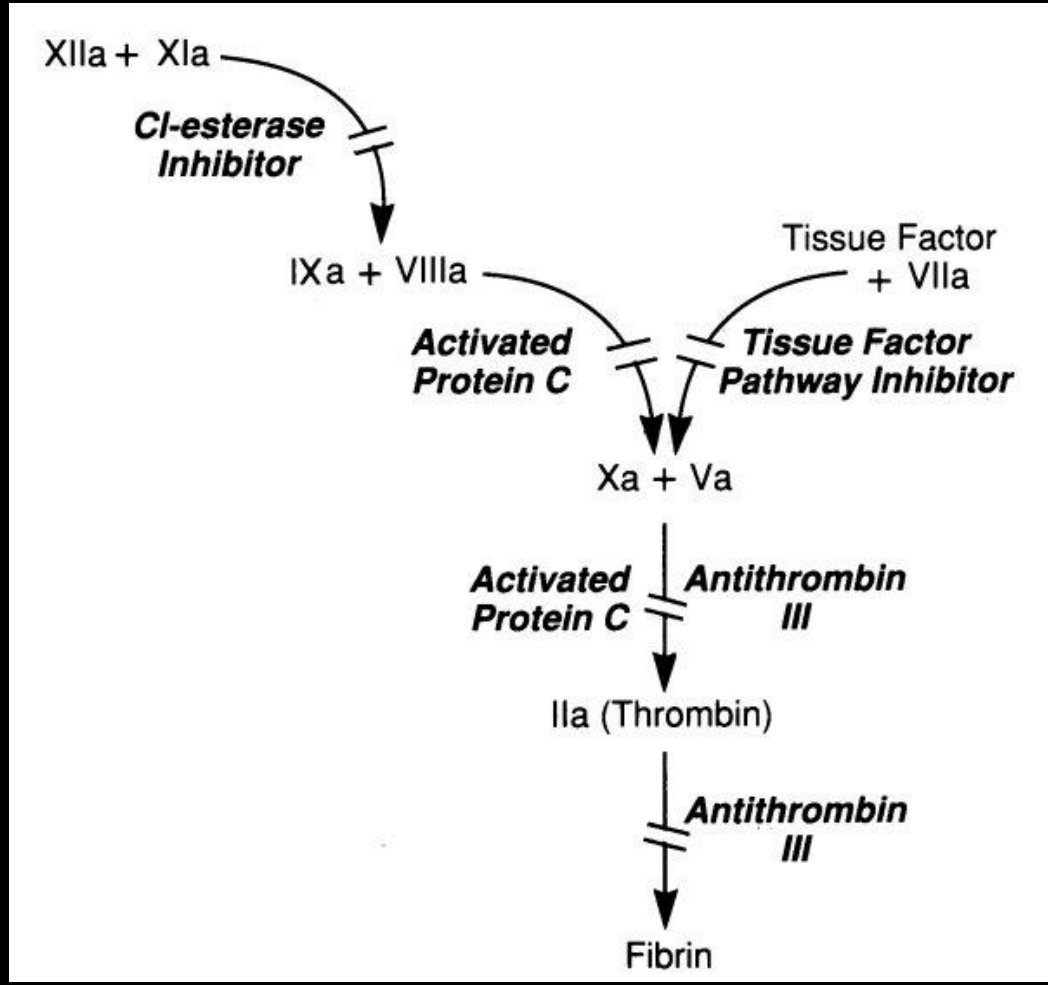

- Coagulation at the beginning of the 20th century. **A:** Early theories of blood coagulation are thought to have been based on the writings of *Plato*, who postulated that fibrin was a circulating substance that formed a clot at sites when it left the body and became cooled. By the mid 1800s, it was recognized that blood clotted at physiologic temperatures and resulted from the action of thrombin on fibrinogen. **B:** *Morawitz* integrated the work of a number of investigators in his theory of coagulation published in 1905. The extract known as *tissue thromboplastin* is now understood to be composed of anionic phospholipids and the membrane-bound glycoprotein, tissue factor. Phospholipids form the surface on which coagulation reactions take place, while tissue factor is the physiologic activator of factor VII. All theories of coagulation recognized the ability of thrombin to clot fibrinogen.

# CLOTTING CASCADE AND PROPAGATION OF THE CLOT

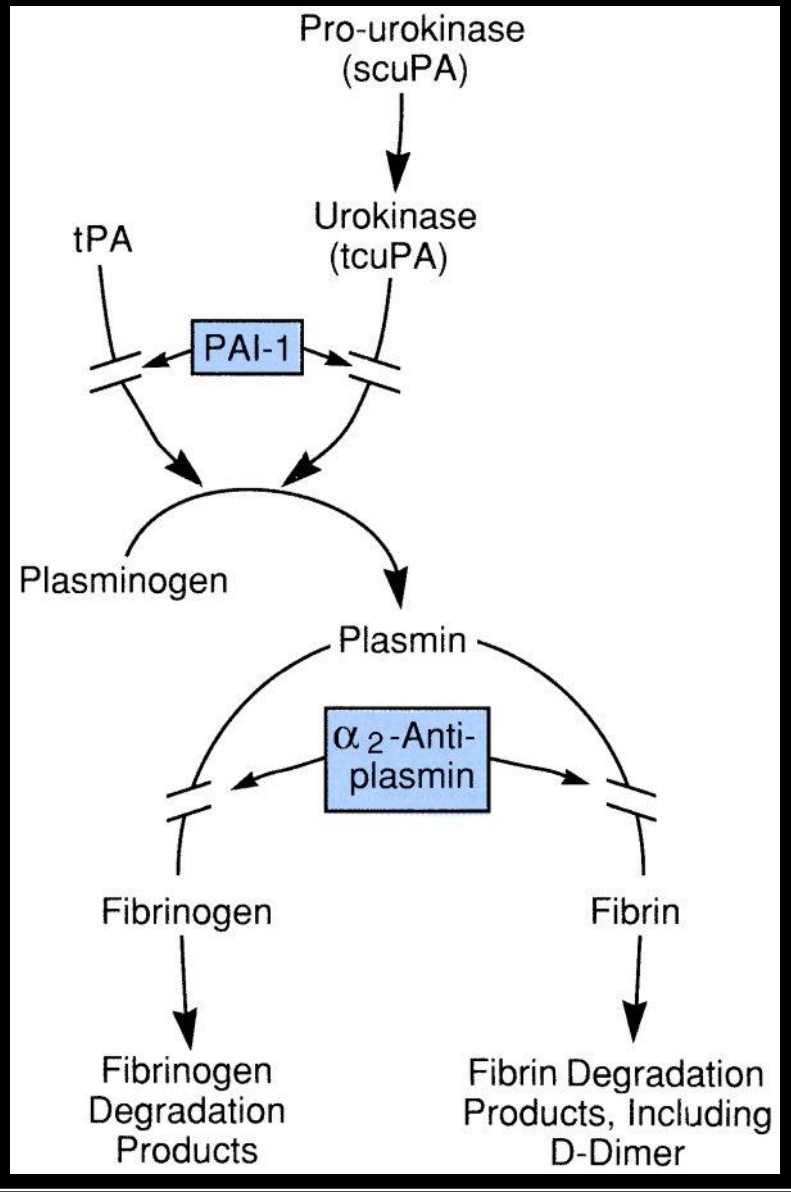
- Crossover scheme of coagulation. After it was recognized that factor VIIa could activate factor IX, a crossover pathway was added to the coagulation scheme



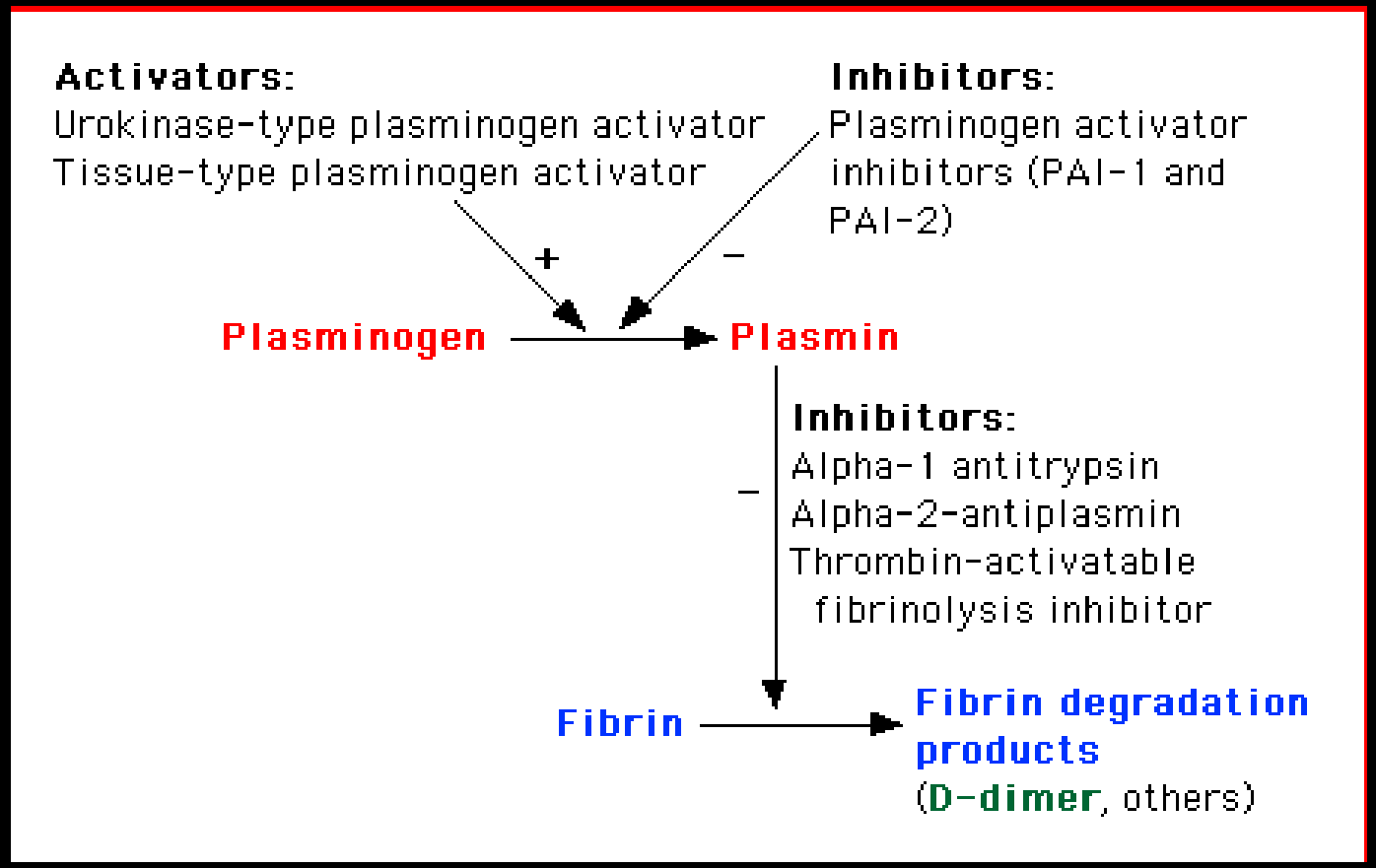
# Coagulation Inhibitors



Fibrinolytic system pathways.
The two major activators of the fibrinolytic system are tissue-type and urokinase-type plasminogen activators (tPA and uPA, respectively).



# The fibrinolytic pathway



# Tests of Haemostatic Function

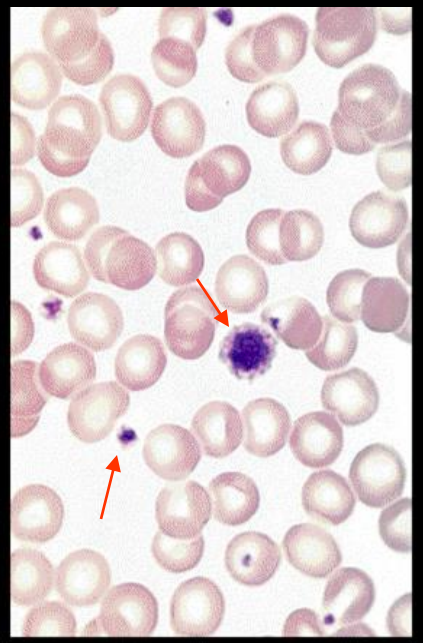
It is critically importance of considering the *history, physical examination, and screening tests* as a complementary facets of the clinical approach to individuals with suspected systemic coagulopathies. Each part alone is inadequate and may actually be misleading.

# Tests of Haemostatic Function

- Platelet count
- Bleeding time
- Prothrombin time (PT)
- Activated Partial Thromboplastin Time (aPTT)

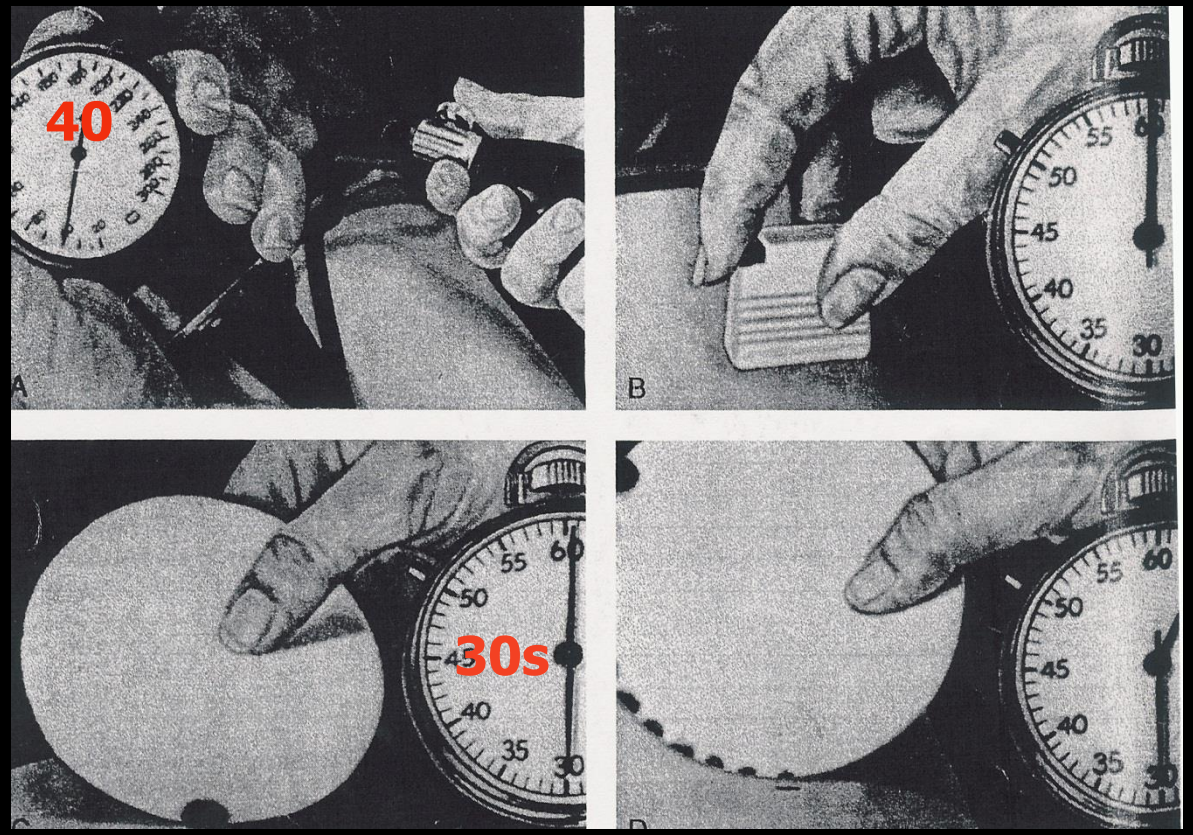
# PLATELET COUNT

- **The normal blood platelet count is 150,000 to 450,000/ul. It has been reported that among Mediterranean patients, the reference platelet count range may be relatively low (125 to 300 vs. 150 to 450 x $10^9$/L) (BLOOD.HANDIN,2003)**



# BLEEDING TIME

- The bleeding time is widely recognized as the best screening test of *in vivo* primary hemostasis.
- The standard Ivy method has been modified( by supplanted newer disposable automated products) to improve sensitivity and reproducibility.



# PROTHROMBIN TIME (PT)

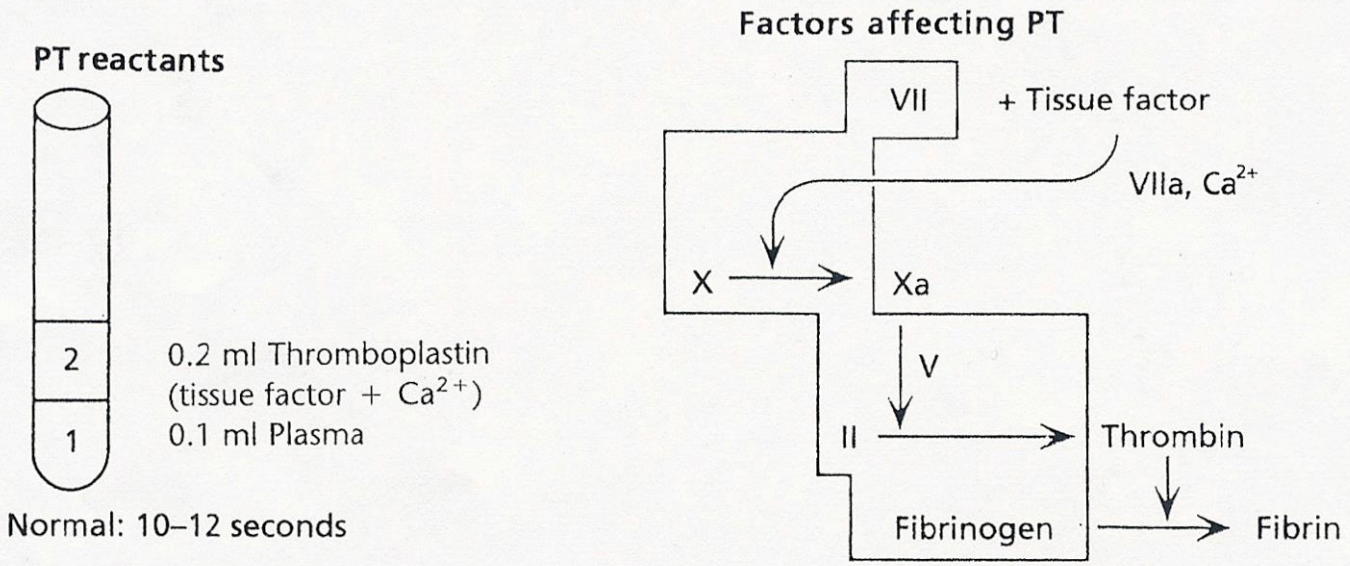



**FIGURE 18.4.** The prothrombin time (PT) is sensitive to isolated or combined deficiencies of factors VII, X, V, and II (prothrombin) and fibrinogen. (Adapted from Burns ER, ed. Laboratory tests of hemostasis. In: *Clinical management of bleeding and thrombosis*. Boston: Blackwell Scientific, 1987:43–56, with permission.)

# PROTHROMBIN TIME (PT)

- The PT measures the activity of extrinsic and common pathways of coagulation.
- The sensitivity of the PT in detecting coagulation factor deficiencies may vary with the reagents used to perform these tests.Thromboplastins prepared from human brain are generally more responsive to reduction in the coagulation factors affected by the PT than those prepared from rabbit Brian. It was because this marked variability of responses to different thromboplastins between laboratories that the international normalized ratio (INR) was adopted to standardize reporting of the PT in individuals receiving oral anticoagulation.
- The PT ,which is variably prolonged with deficiencies of factors VII, X, V, II, I, is significantly affected by factor VII levels of less than 50% or by more severe deficiencies (levels less than 30%) of the other factors.

# ACTIVATED PARTIAL THROMBOPLASTINTIME (aPTT)

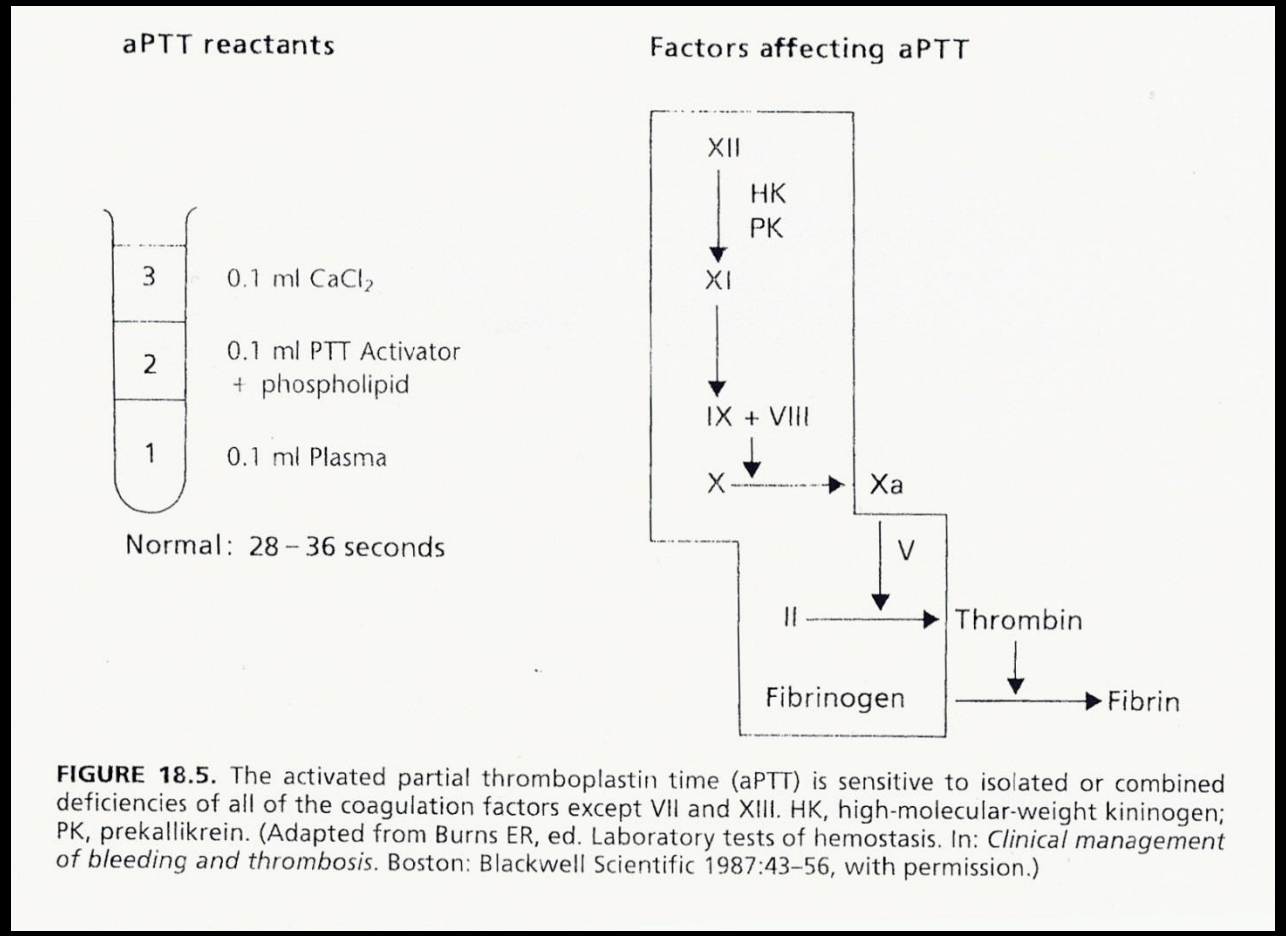
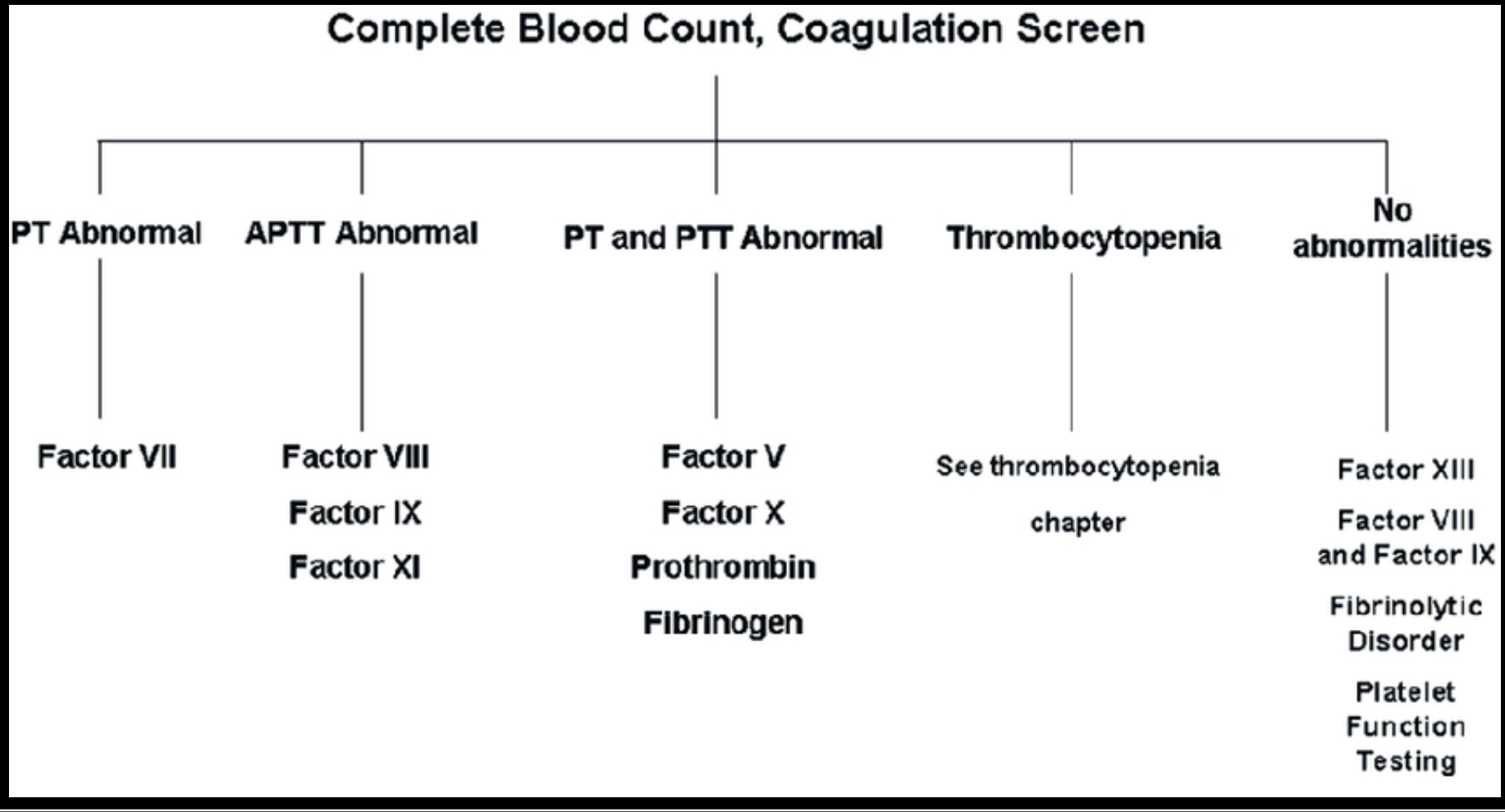


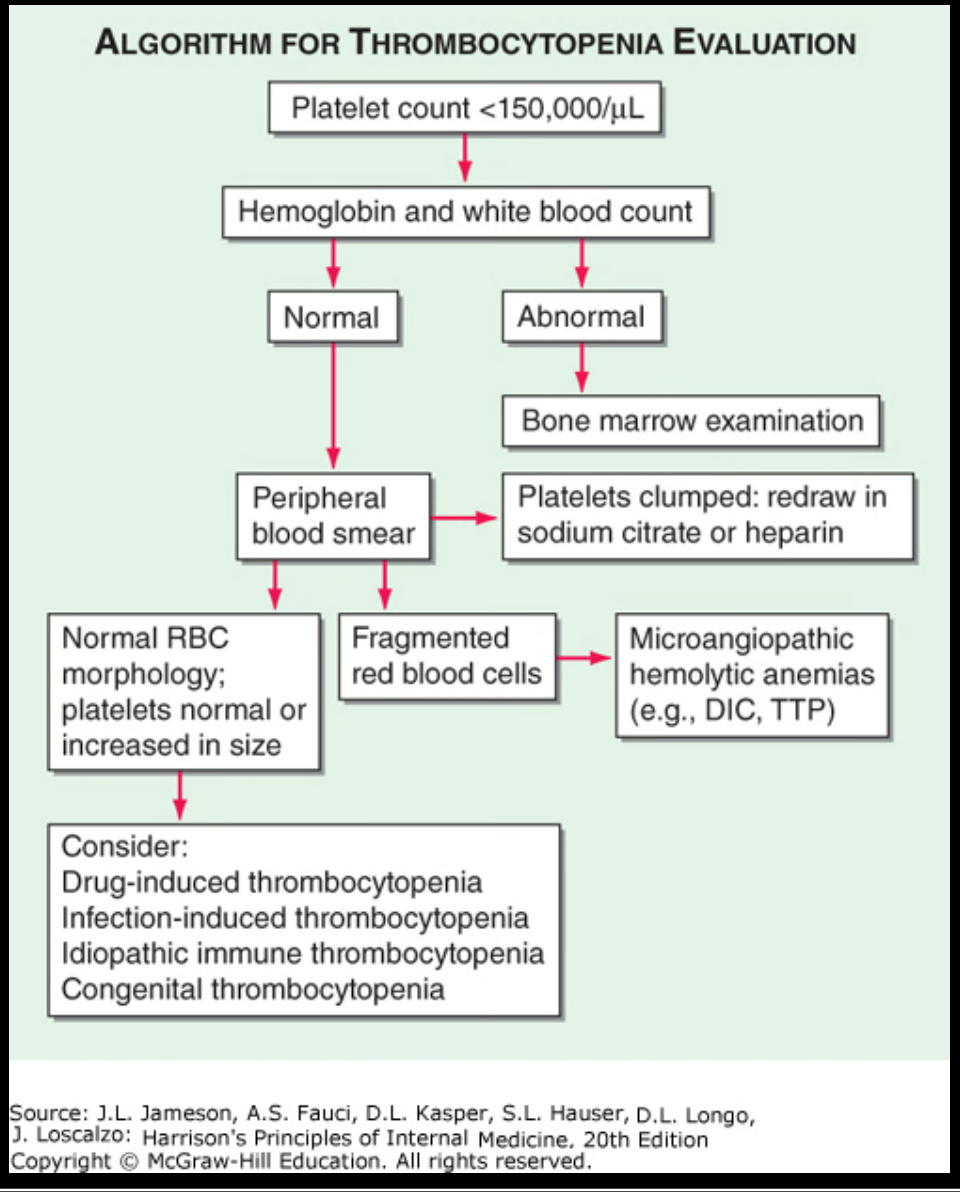

**FIGURE 18.5.** The activated partial thromboplastin time (aPTT) is sensitive to isolated or combined deficiencies of all of the coagulation factors except VII and XIII. HK, high-molecular-weight kininogen; PK, prekallikrein. (Adapted from Burns ER, ed. Laboratory tests of hemostasis. In: *Clinical management of bleeding and thrombosis*. Boston: Blackwell Scientific 1987:43–56, with permission.)

# ACTIVATED PARTIAL THROMBOPLASTINTIME (aPTT)

- The aPTT assesses the integrity of the intrinsic and common pathways of coagulation.
- The sensitivity of the aPTT in detecting coagulation factor deficiencies may vary with the reagents used to perform these test. Various manufacturers, aPTT reagents and even reagents lots from the same manufacturer show considerable variation in response to heparin; in view of these considerations, every coagulation laboratory must determine its own reference standard time for aPTT and must perform mixing studies to establish the sensitivities of the reagents used to detect specific factor deficiency states.
- The aPTT is variably prolonged with deficiencies of coagulation factors except factor VII. In general, factor VIII or factor IX activities of less than 30% should be detectable on screening by clear prolongations of the aPTT.

# Bleeding Disorders Diagram






Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

# Evaluation of Prolonged Bleeding Time in the Absence of Thrombocytopenia

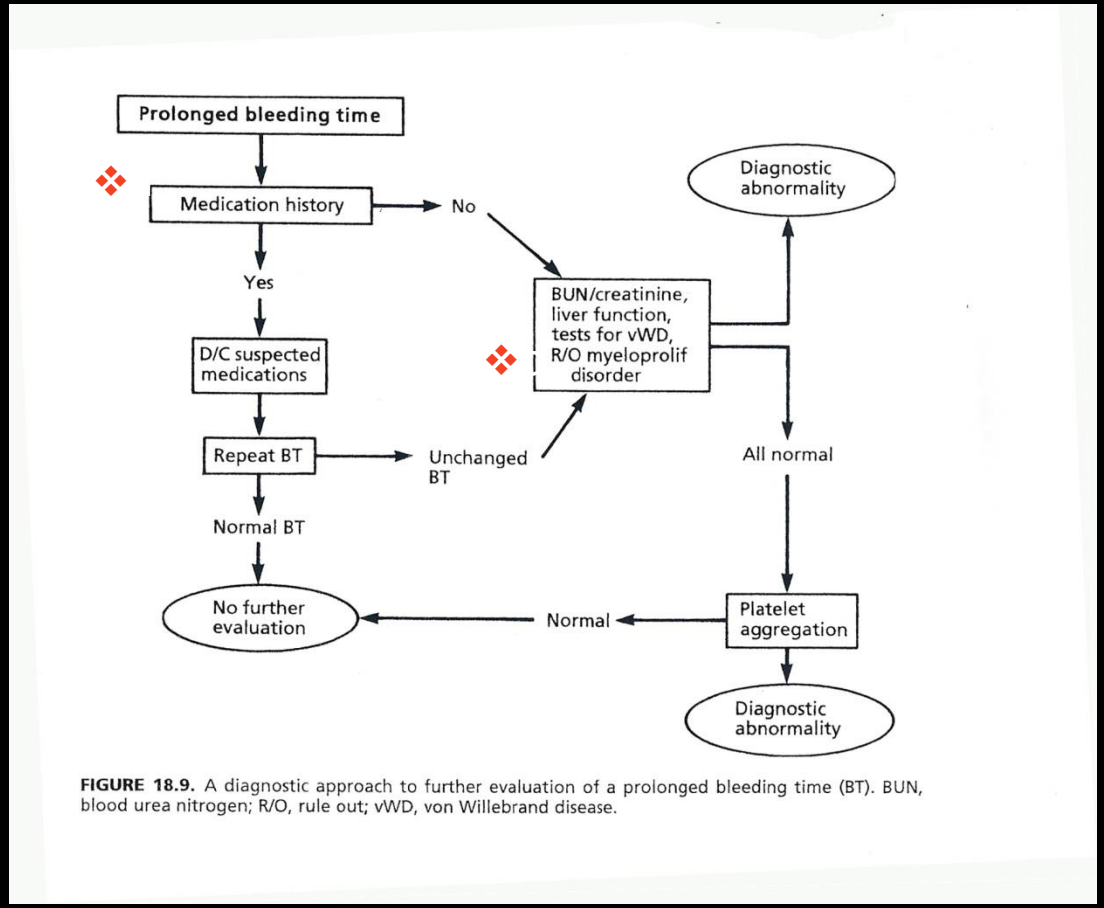



**FIGURE 18.9.** A diagnostic approach to further evaluation of a prolonged bleeding time (BT). BUN, blood urea nitrogen; R/O, rule out; vWD, von Willebrand disease.

# Introduction

Abnormal bleeding may result from:

- Vascular disorders
- Thrombocytopenia
- Defective platelet function
- Defective coagulation

# VASCULAR DISORDER

# Vascular Bleeding Disorder

- **The vascular disorders are a heterogeneous group of conditions characterized by easy bruising and spontaneous bleeding from small vessels may be inherited or acquired.**
- **The underlying abnormality is either in the vessels themselves or in the perivascular connective tissues.**
- **Most cases of bleeding caused by vascular defect alone are not severe.**
- **Frequently the bleeding is mainly in the skin causing petechiae, ecchymoses or both.In some cases there is also bleeding from mucous membranes.**
- **In these conditions the standard screening tests are normal.**

# Vascular Bleeding Disorders

**Hereditary**
- hereditary haemorrhagic telangiectasia
- Ehlers–Danlos syndrome
- Marfan's syndrome
- osteogenesis imperfecta
- Fabry's syndrome

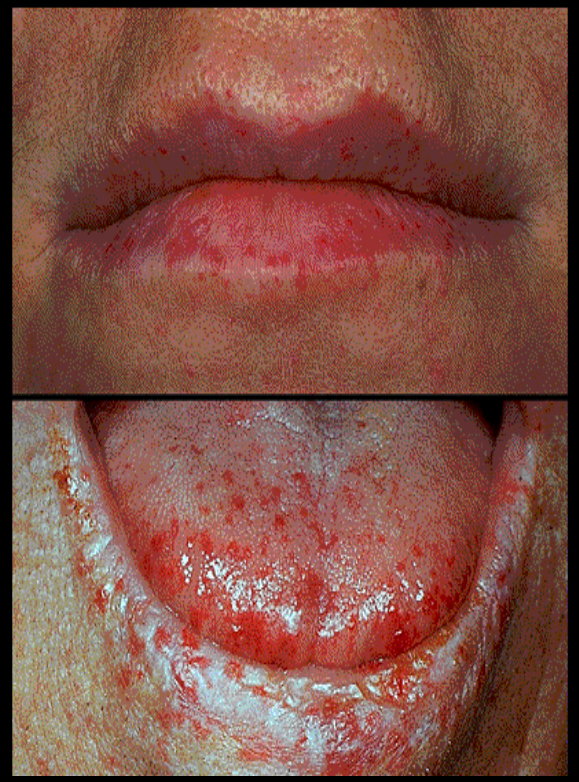
**Infections**
- bacterial
- viral
- rickettsial

**Allergic**
- Henoch–Schönlein syndrome
- drugs
- food

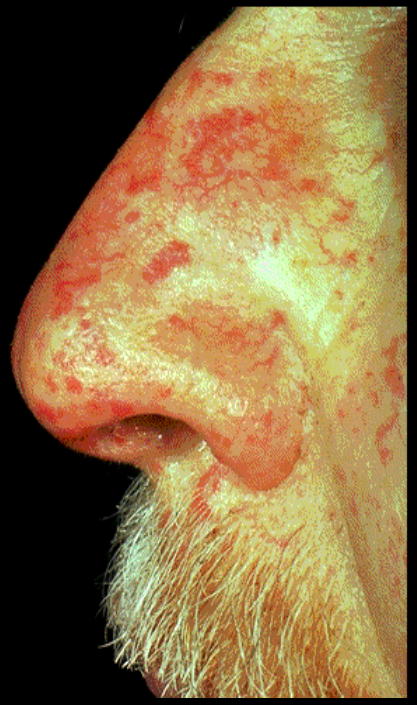
# Inherited vascular disorders

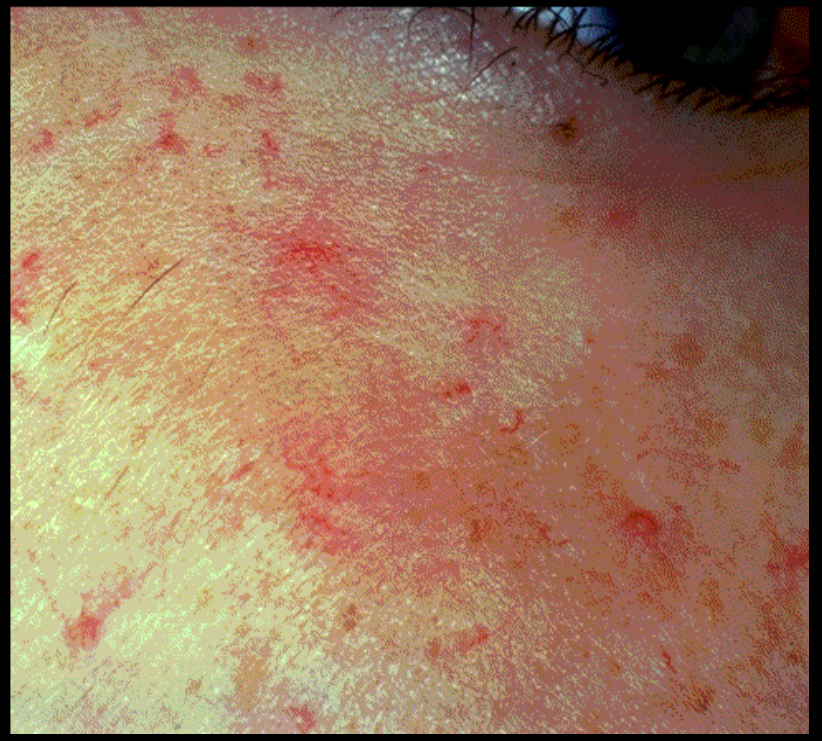
## Hereditary haemorrhagic telangiectasia

- In this uncommon autosumal dominant disorder there are dilated microvascular swellings which appear during chilhood and become more numerous in adult life.
- The telangiectasia develop in the skin,mucos memberanes and internal organ (GI,Pulmonary)



# Hereditary haemorrhagic telangiectasia

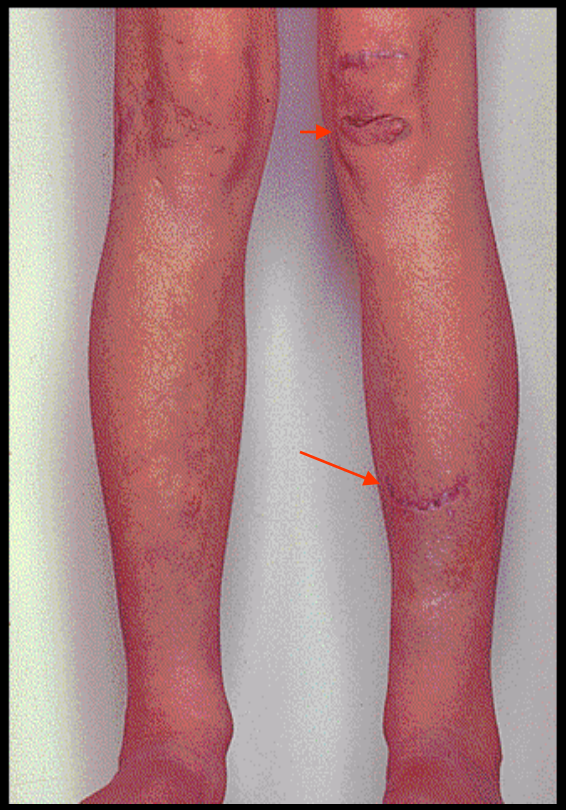




# Inherited vascular disorders

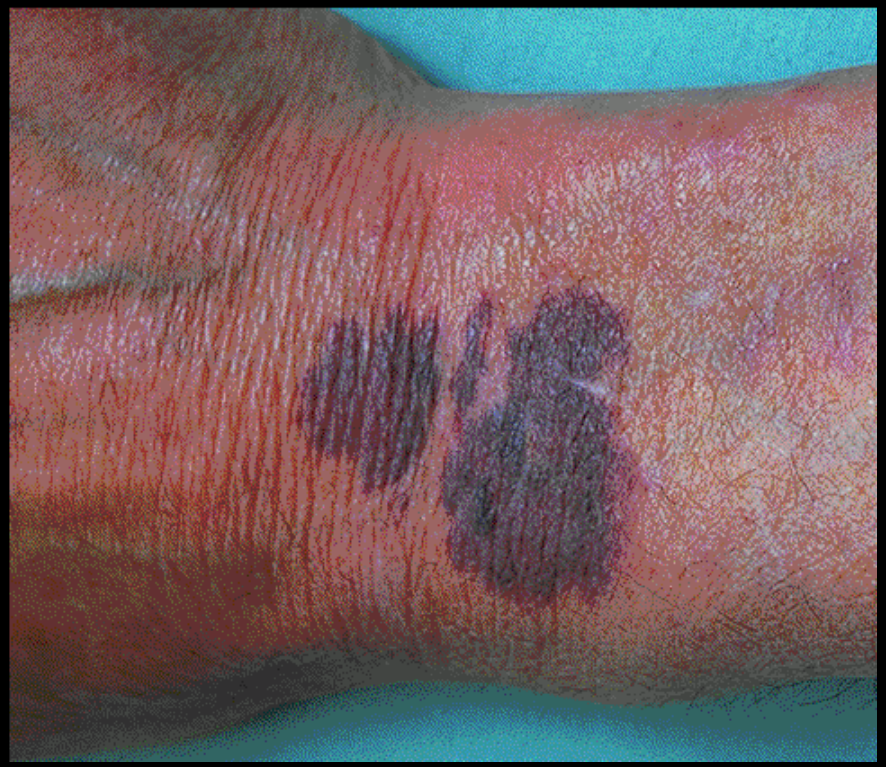
## Ehlers-Danlos syndrome

- There are hereditary collagen abnormalities with purpura due to defective platelet aggregation,hyperextensi-bility of joints and hyperelastic friable skin.
- Mild cases may present with superficial brusing and purpura following minor truma.



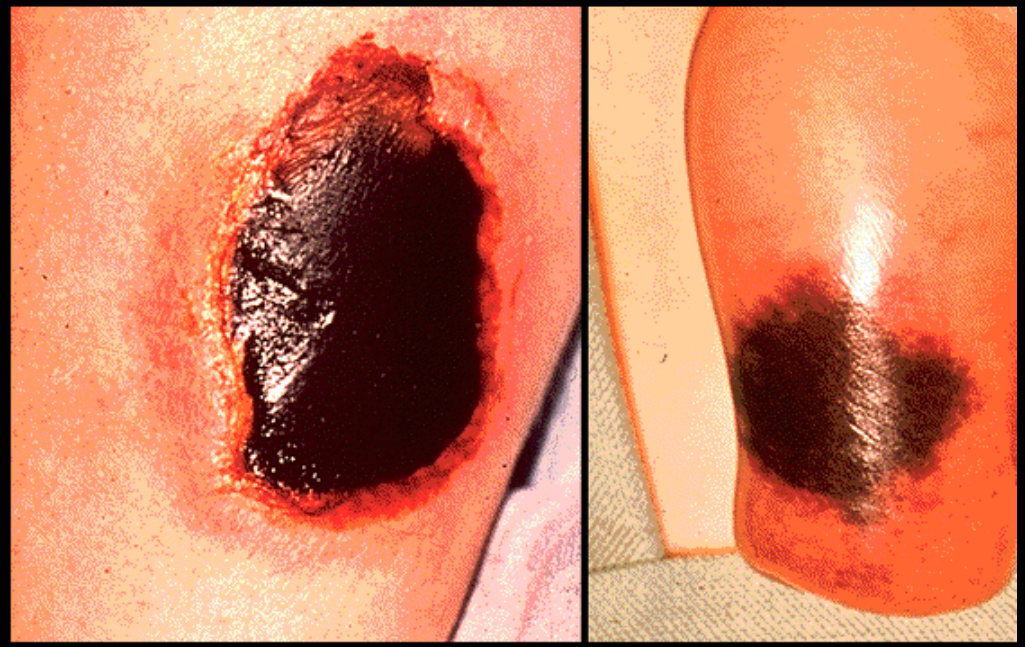
# Acquired vascular defects

## Senile purpura



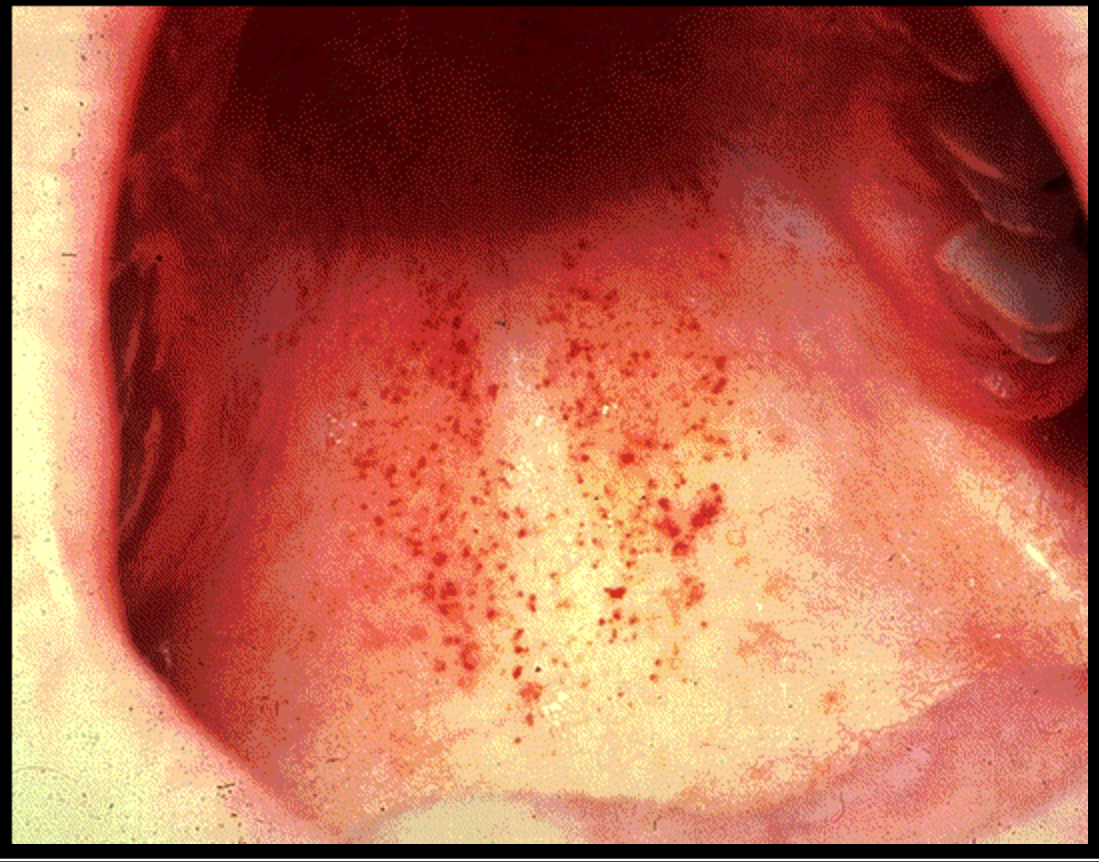
# Acquired vascular defects
# Purpura associated with infection

**Purpura fulminant**
**Varricella infection**



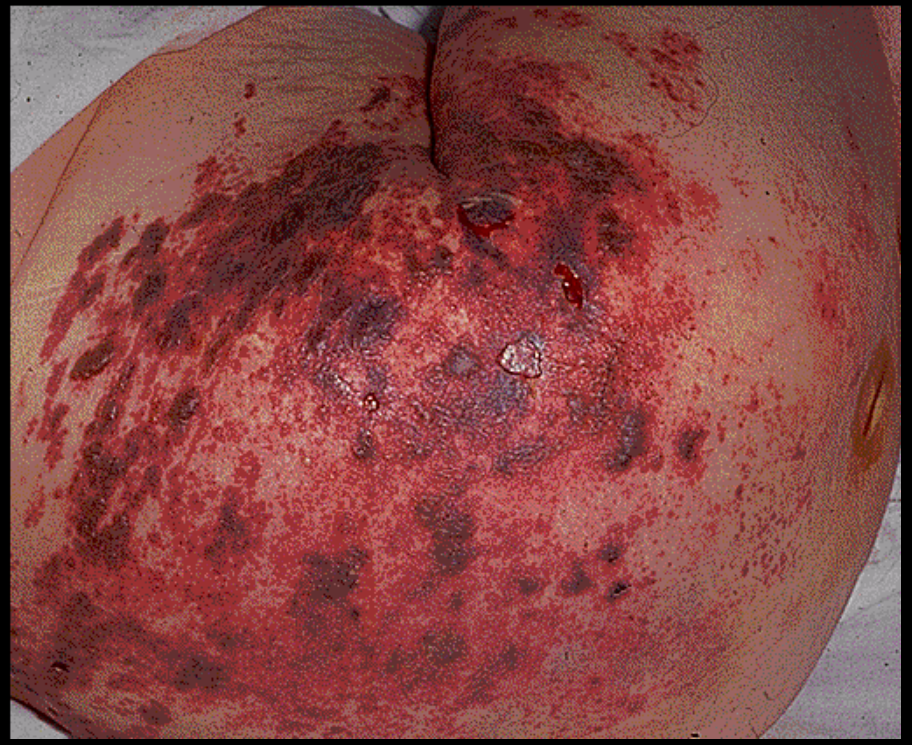
# Acquired vascular defects
# Purpura associated with infection

Infectious Mononucleosis



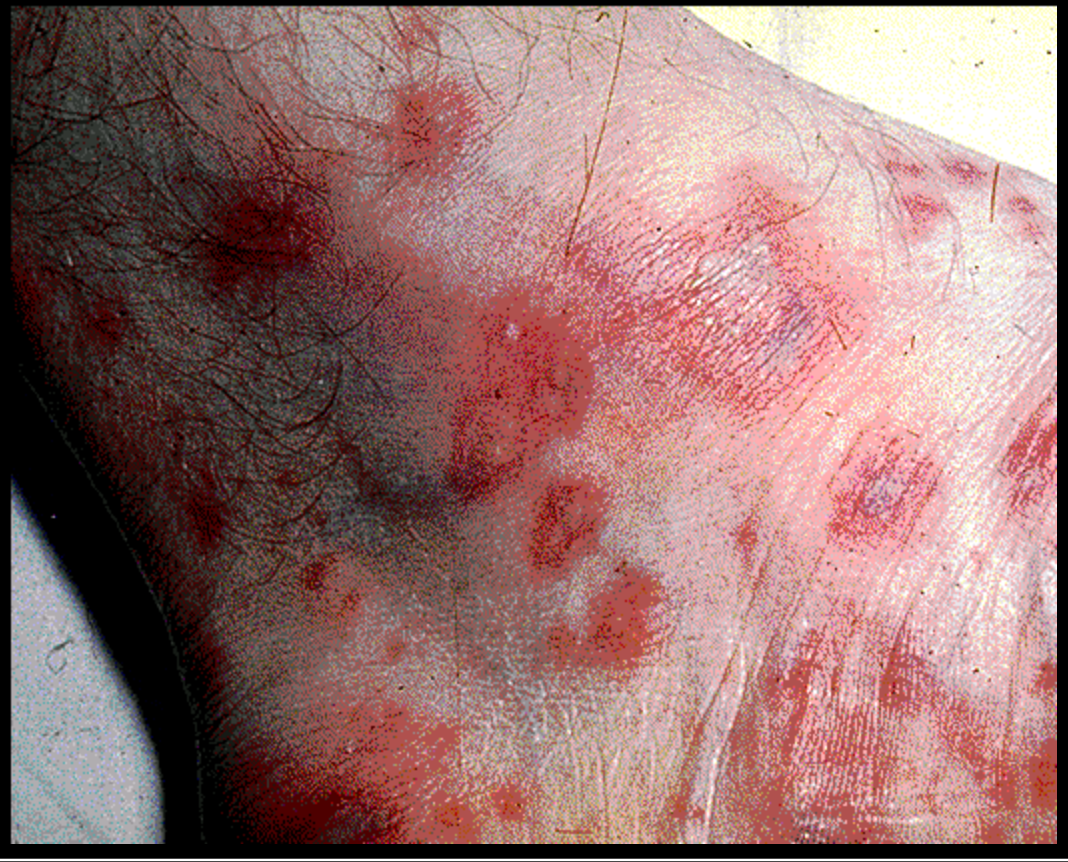
# Acquired vascular defects
# Purpura associated with infection

**Herpes zoster**



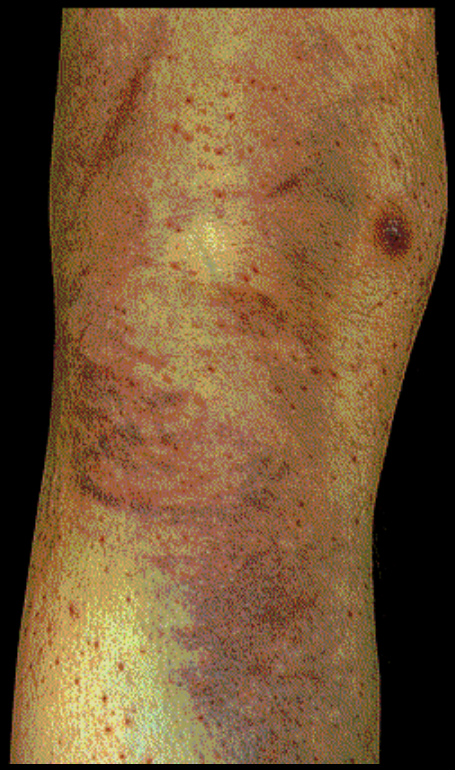
# Acquired vascular defects
# Purpura associated with infection

**Meningococcemia**

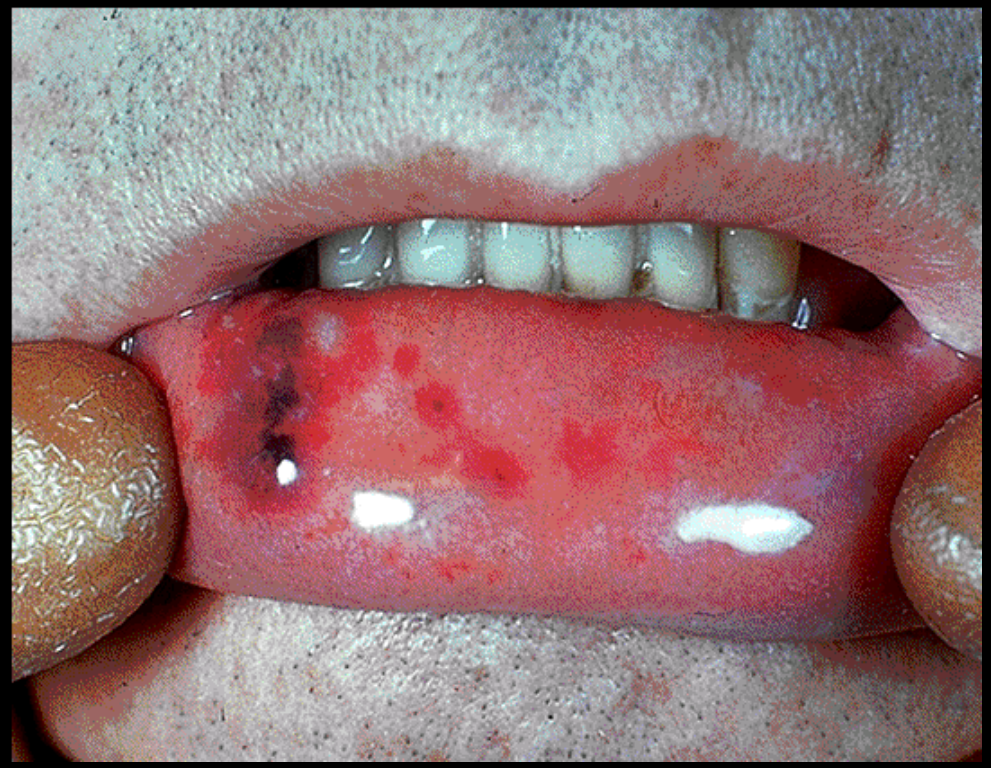


# Acquired vascular defects
# Scurvy

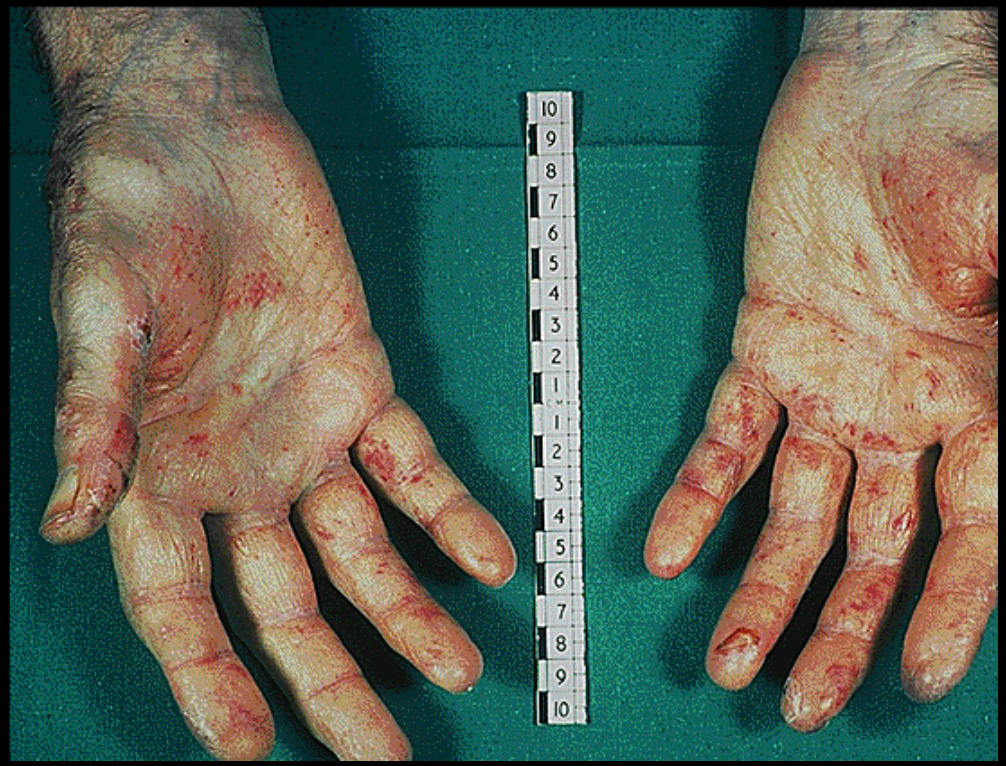
**Perifollicular petechiae**



# Acquired vascular defects
# Multiple myeloma

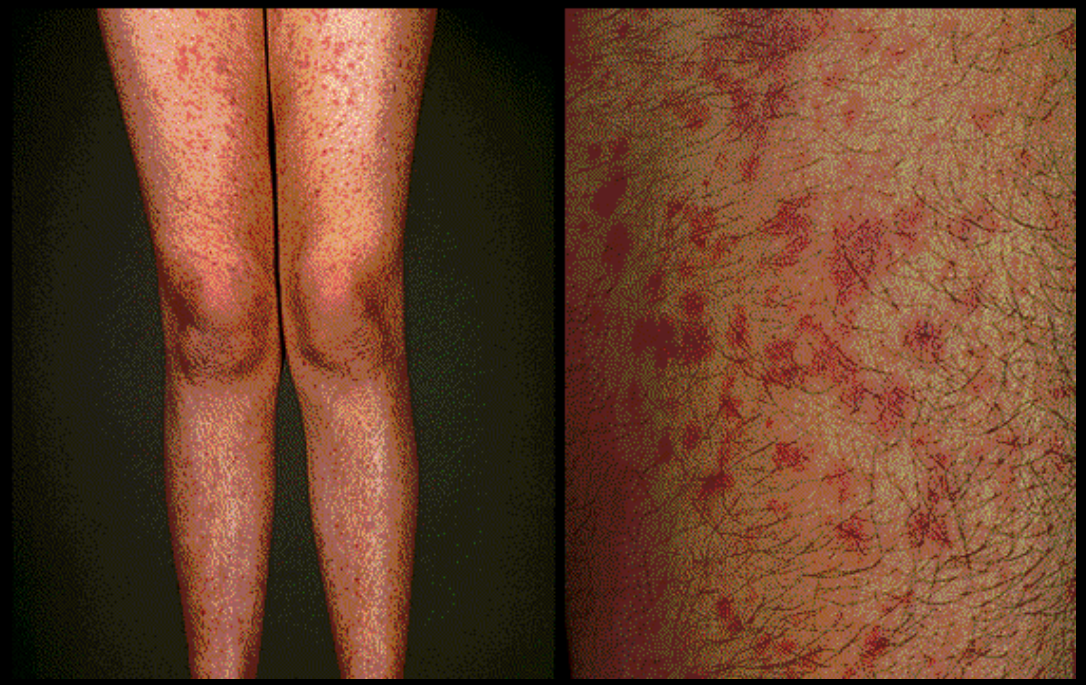


# Acquired vascular defects
# Amyloidosis



# Acquired vascular defects Henoch-Schönlein syndrome

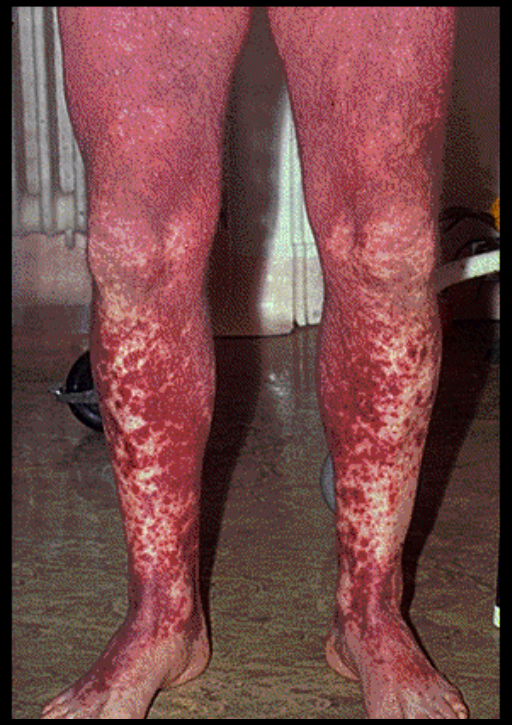
- Is usually seen in children and follows an acute infection.
- It is an immunoglobulin A (IgA)-mediated vasculitis.
- The characteristic purpuric rash accompanied by localized oedema and itching is usually most prominent on the buttocks and extensor surfaces of lower leg and elbows



# Acquired vascular defects

## Henoch-Schönlein syndrome

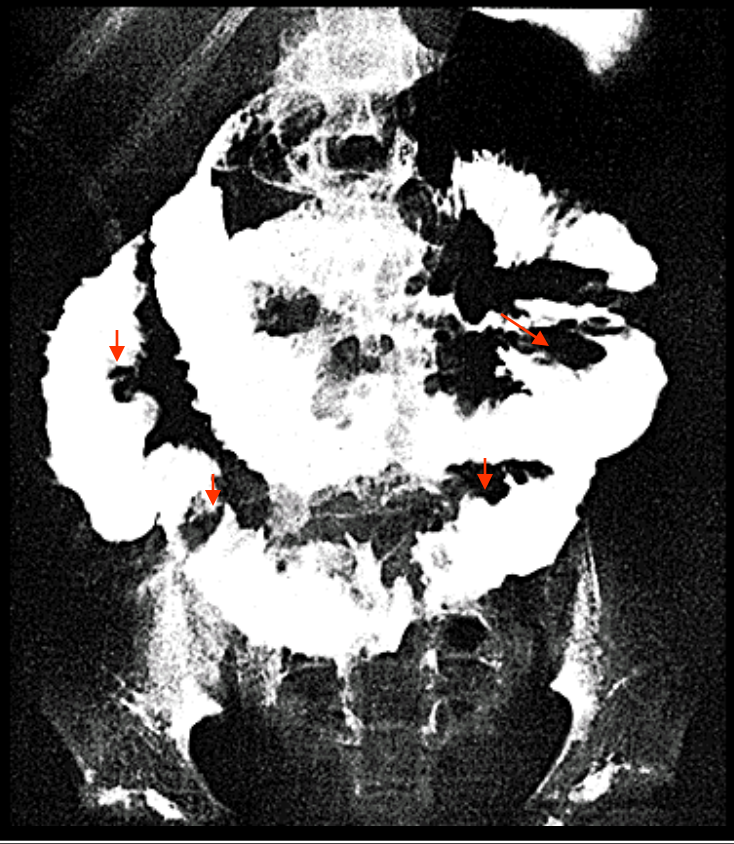
- Painful joint swelling, haematuria.and abdominal pain may also occur
- It is usually a self-limiting codition but occassional patients develop renal failure



# Acquired vascular defects

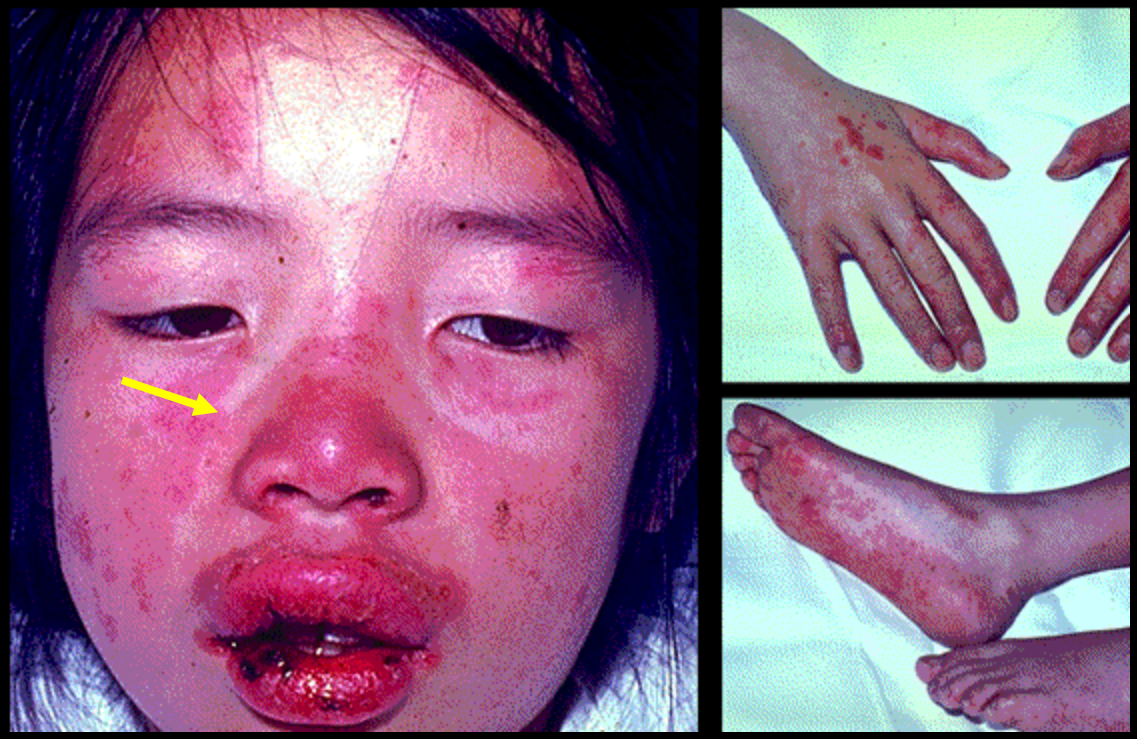
## Henoch-Schönlein syndrome

**Thumb print effect**



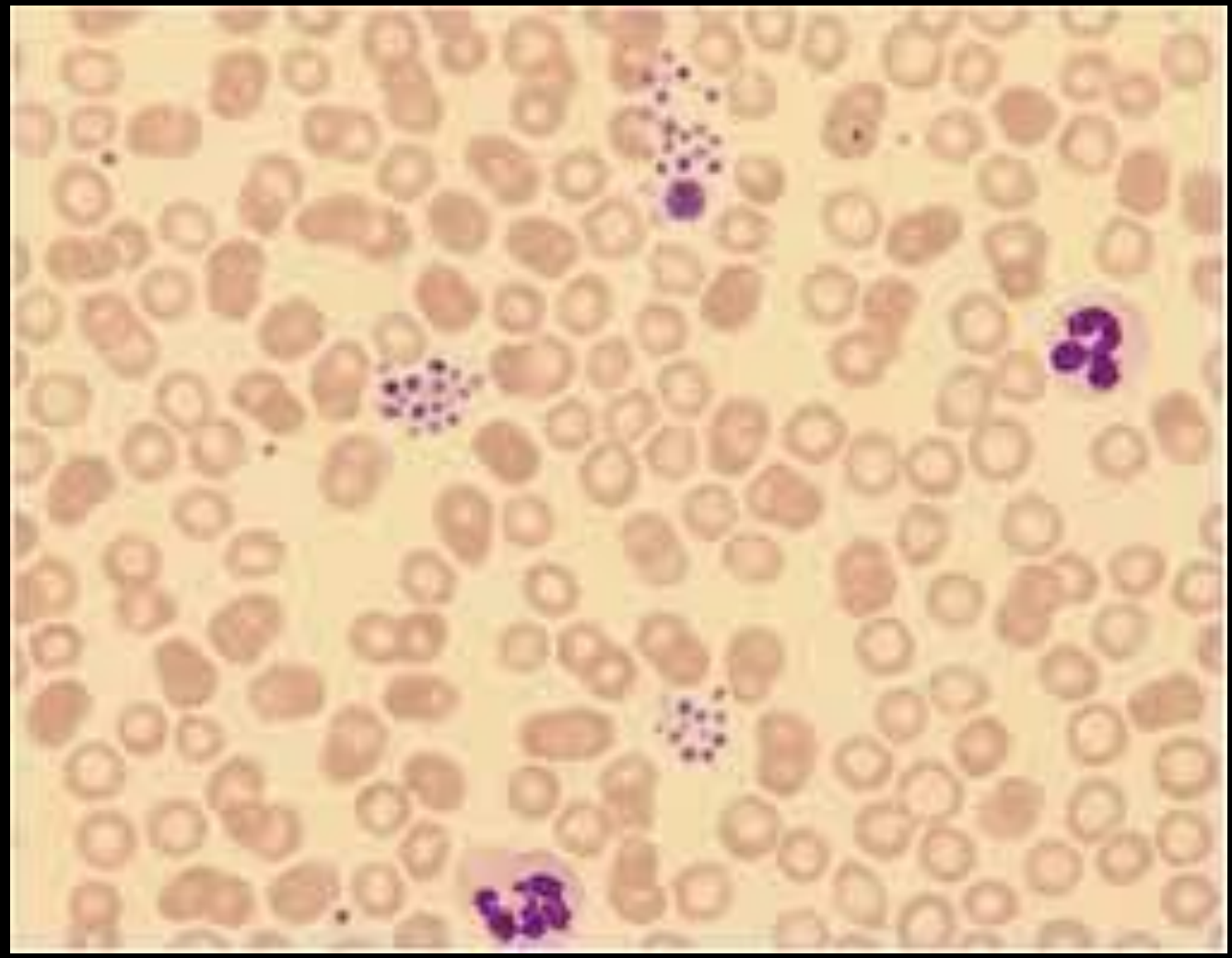
# Acquired vascular defects
# Systemic lupus erythematous

**Butterfly rash**



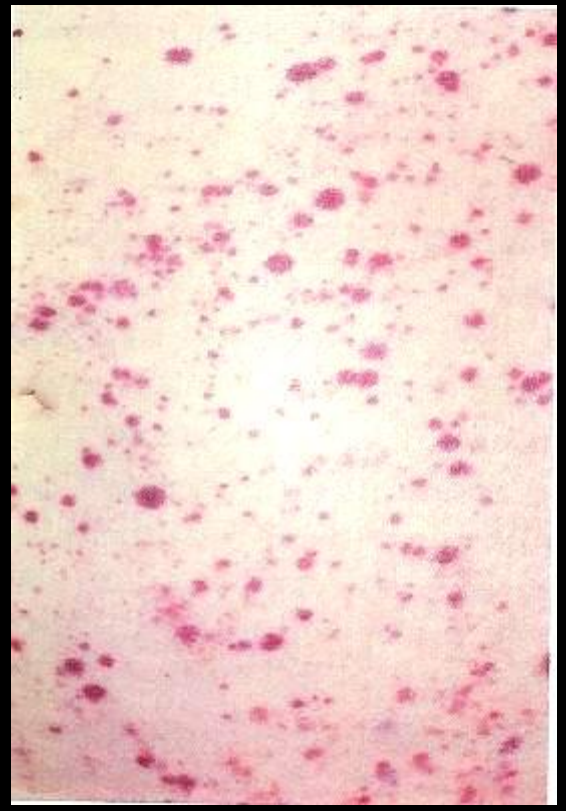
# PLATELET DISORDER

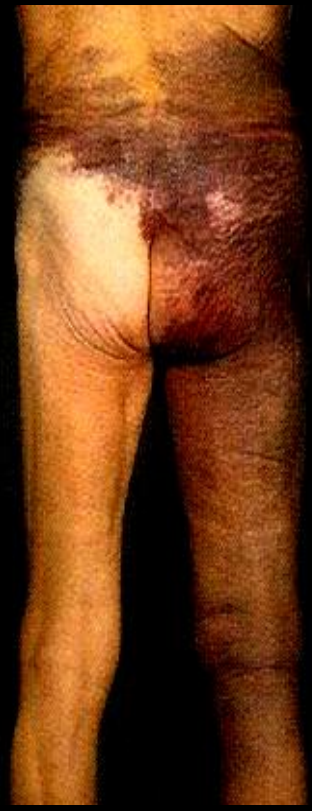
## Pseudo thrombocytopenia



# Thrombocytopenia

- Abnormal bleeding associated with thrombocytopenia or abnormal platelet function is characterized by spontenous skin purpura and mucosal hemorrhage and prolonged bleeding after trauma.





# Causes of thrombocytopenia

- *Failure of platelet production*
  - Selective megakaryocyte depression
  - Part of general bone marrow failure
- *Increased consumption of platelets*
  - Immune,(ITP)
  - Non-Immune,(DIC,TTP)
- *Abnormal distribution of platelet*
  - Splenomegaly
- *Dilutional loss*
  - Massive transfusion of stored blood to bleeding patients

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# Failure of platelet production

- This is the most common cause of thrombocytopenia and is usually part of a generalized bone marrow failure.
- Selective megakatyocyte depression may result from drug toxicity or viral infection.
- Rarely, it is congenital due to mutation of c-MPL thrombopoietin receptor, in association with absent radii,or in May-Hegglin or Wiscott-Aldrich syndrome.
- Diagnosis of these causes of thrombocytopenia is made from the clinical history, peripheral blood count, the blood film and the bone marrow examination.

# Increased consumption of platelets

**Immune**

•autoimmune(idiopathic)

associated with systemic lupus erythematosus ,chronic - lymphocytic leukemia or lymphoma

• infection: HIV,other viruses,malaria

• drug-induced: heparin

• post-transfusional purpura

• feto-maternal alloimmune thrombocytopenia

# Autoimmune ( Idiopathic) thrombocytopenic purpura

- Chronic ITP
- Acute ITP

## *Chronic ITP*

- This is a relatively common disorder.
- The highest incidence has been considered to be in women aged 15-50 years although some reports suggest an increasing incidence with age.
- It is the most common cause of thrombocytopenia without anaemia or neutropenia.
- It is usually idiopathic but may be seen in association with other diseases;(NHL,SLE,HIV)

# Pathogenesis

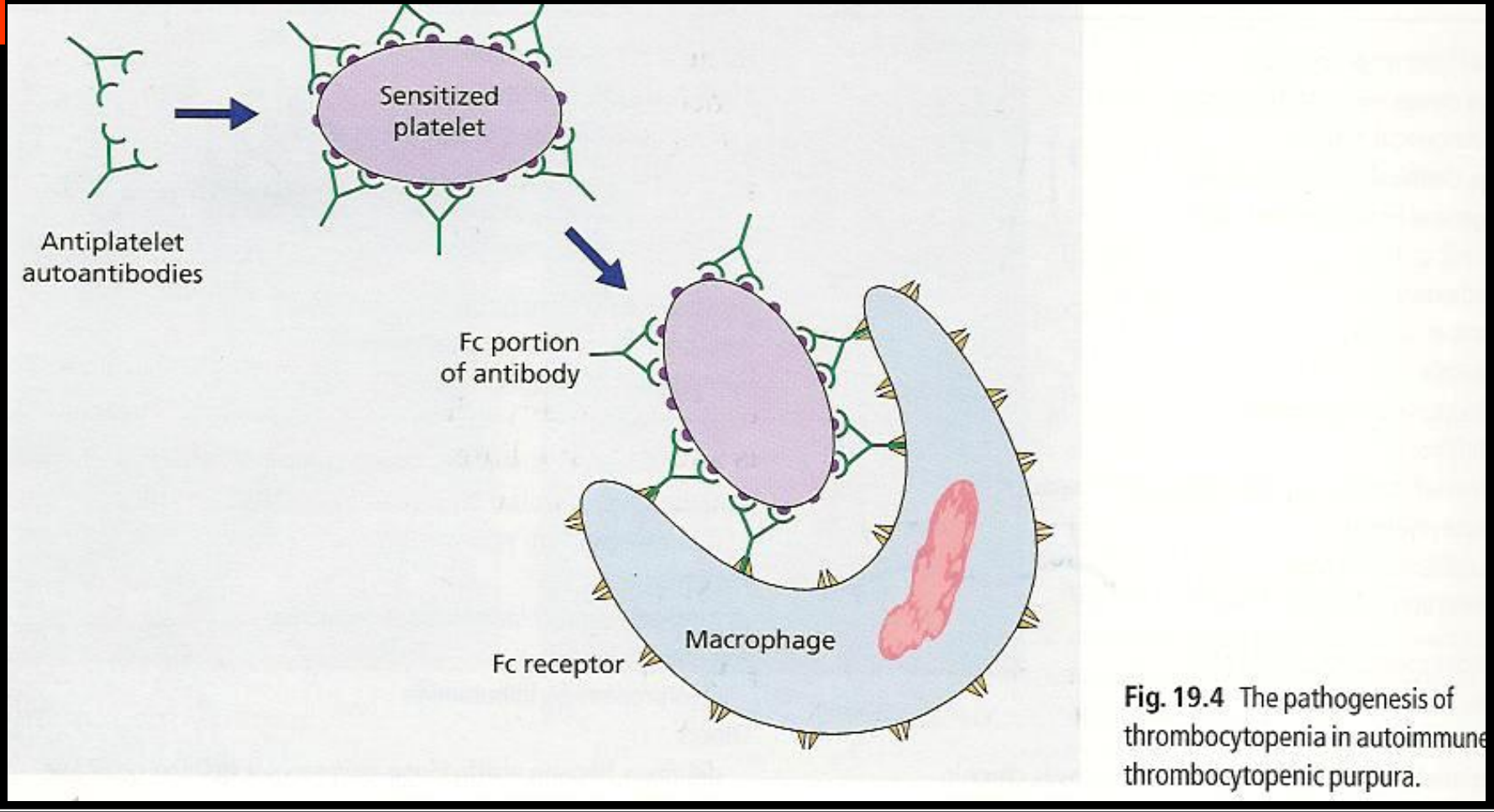



**Fig. 19.4** The pathogenesis of thrombocytopenia in autoimmune thrombocytopenic purpura.

# *Clinical features*

- **The onset is often insidious with petechial hemorrhage, easy bruising and, in women, menorrhagia.**
- **Mucosal bleeding, e.g. epistaxes or gum bleeding, occurs in severe cases but fortunately intracranial hemorrhage is rare.**
- **The severity of bleeding in ITP is usually less than that seen in patients with comparable degrees of thrombocytopenia from bone marrow failure.**
- **Chronic ITP tends to relapse and remit spontaneously so the course may be difficult to predict.**
- **Many asymptomatic cases are discovered by a routine blood count.**
- **The spleen is not palpable unless there is an association disease causing splenomegaly.**

# Diagnosis

- The platelet count is usually 10-50 x $10^9$ /l. The hemoglobin concentration and with cell count are typically normal unless there is iron deficiency anemia because of blood loss.
- The blood film shows reduced numbers of platelets, those present often being large.
- The bone marrow shows normal or increased numbers of megakaryocytes.
- Sensitive tests are able to demonstrate specific antiglycoprotein GPIIb/IIIa or GPIb antibodies on the platelet surface or in the serum in most patient. Platelet-associated IgG assay are less specific.

# *Acute ITP*

- This the most common in children.
- In about 75% of patients the episode follows vaccination or an infection such as chicken pox or infectious mononucleosis.
- Most cases are due to non-specific immune complex attachments.
- Spontaneous remissions are usual but in 5-10% of cases the disease becomes chronic.
- Fortunately, morbidity and mortality in acute ITP is very low.

# Immune destruction of platelet

- Infection
- Post-transfusion purpura:

  Thrombocytopenia occurring about 10 days after a blood transfusion has been attributed to antibodies in the recipient developing against the human platelet antigen-1a on transfused platelet.
- Drug-induced immune thrombocytopenia: Quinine including that in tonic water), quinidine and heparin are particularly common causes.

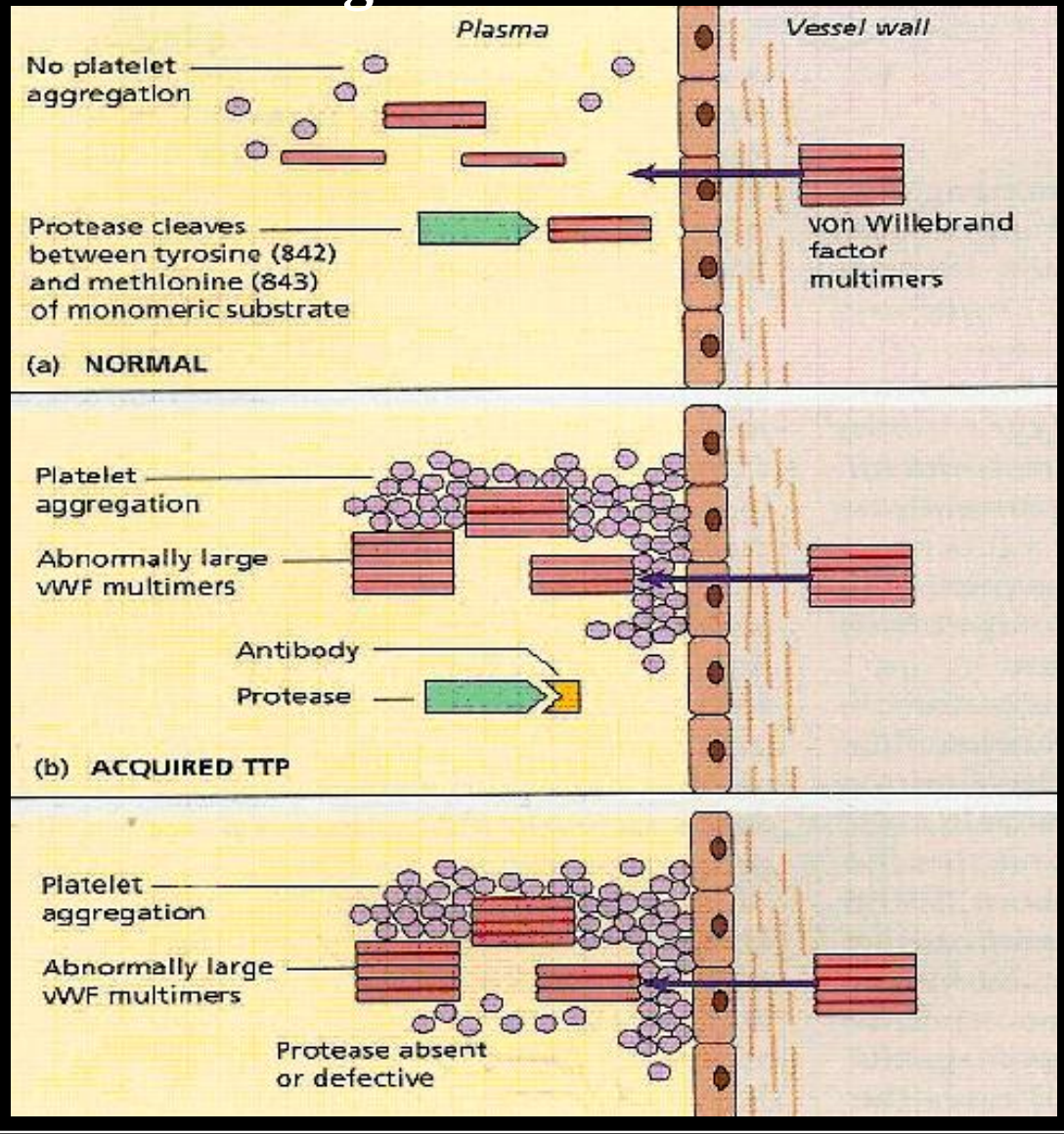
# Increased consumption of platelets

- ✓Disseminated intravascular coagulation
- ✓Increased splenic pooling
- ✓Massive transfusion syndrome
- ✓Thrombotic thrombocytopenic Purpura

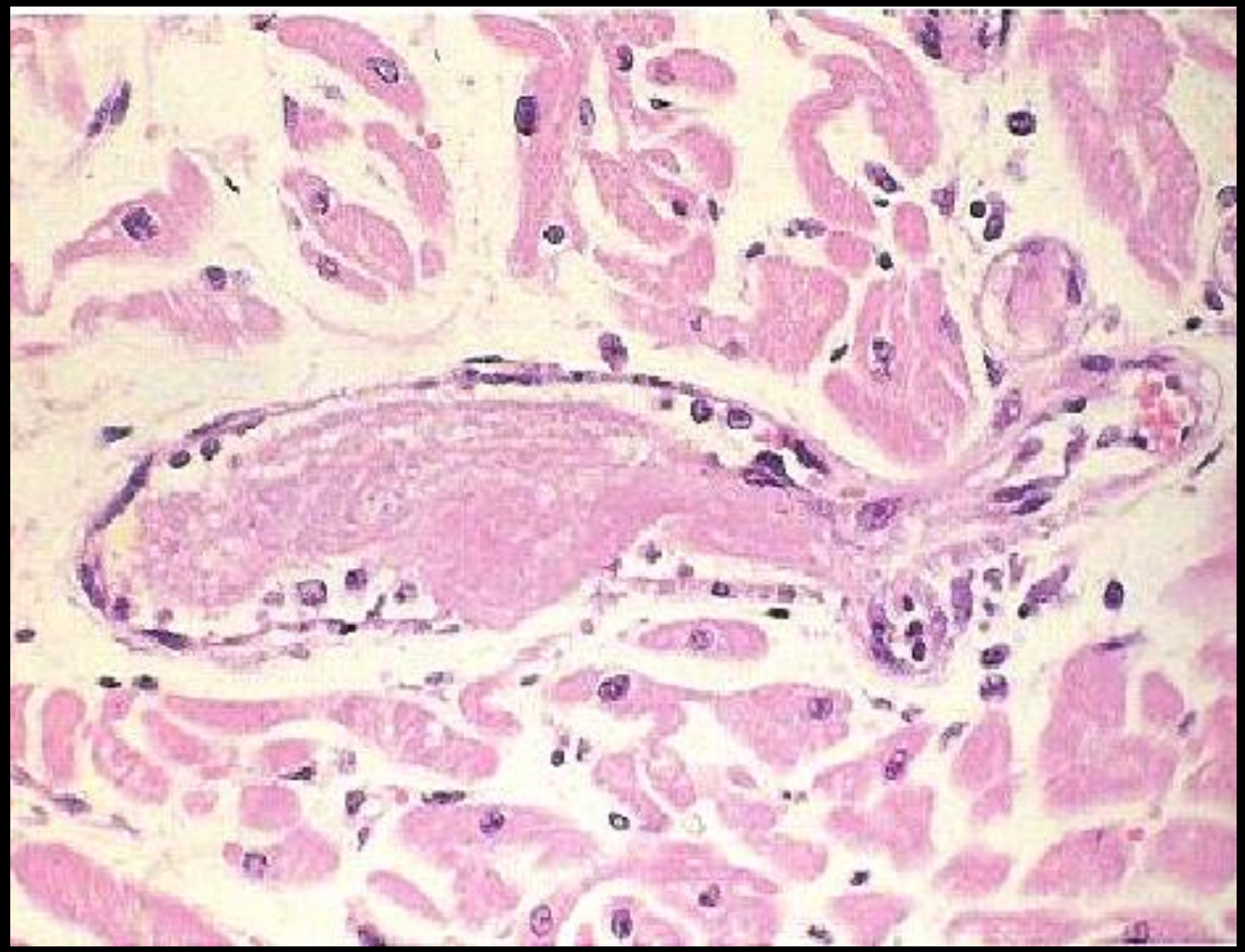
# Thrombotic thrombocytopenic Purpura "pathogenesis"

- TTP occurs in familial or acquired forms.
- There is deficiency of a metalloproteases (caspase) which breaks down high molecular weight multimers of von Willebrand factor (vWF) .
- In familial form this is because of genetic defect whereas in acquired forms it follows the development of an inhibitory antibody, the presence of which may be stimulated by infection.
- High molecular weight vWF multimers in plasma induce platelet aggregation, resulting in microthrombi formation in small vessels.

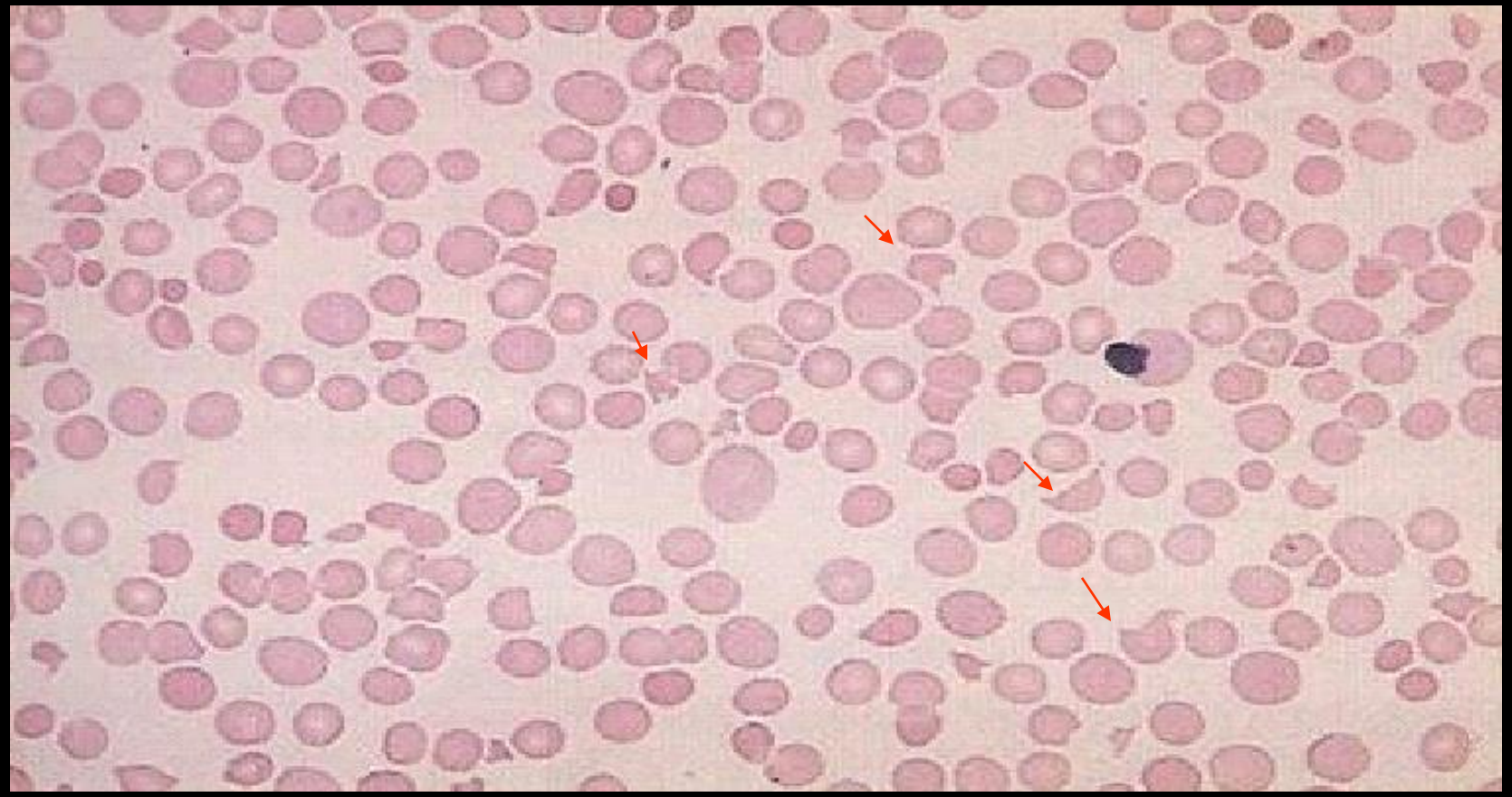
# Pathogensis of TTP



# Pathogensis of TTP



# Pathogensis of TTP



# Clinical features

- Fever
- Severe thrombocytopenia
- Microangiopathic hemolytic anemia
- Neurological symptoms & signs
- Urine abnormalities

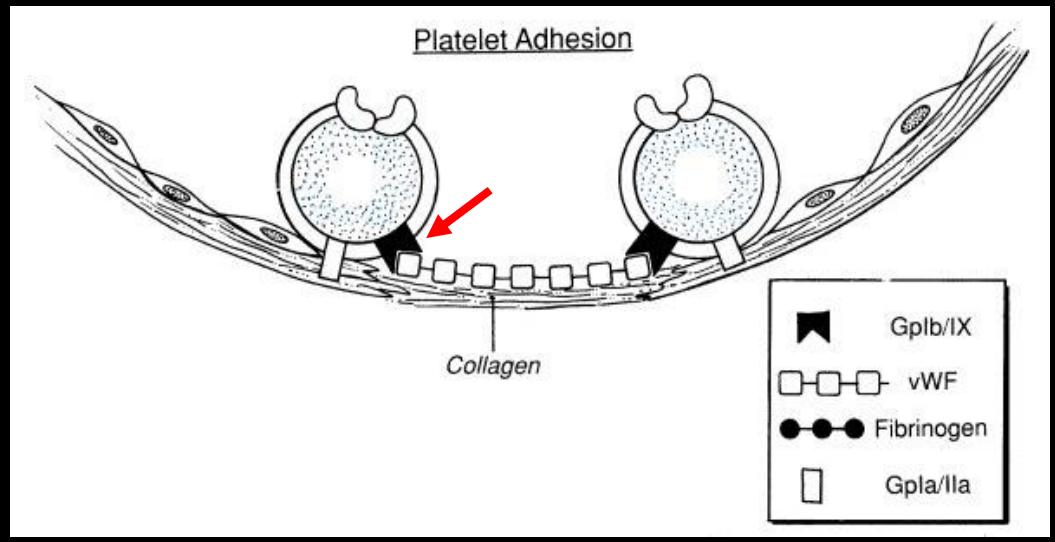
# Disorders of platelet function

- Hereditary disorders
- Acquired disorders

# Hereditary disorders

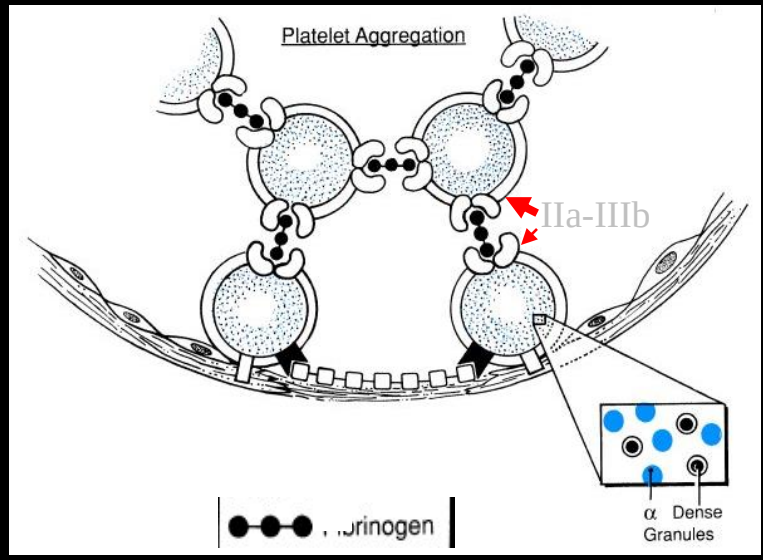
- Bernard-Soulier syndrome
- Thrombasthenia (Glanzmann, s disease)
- Storage pool disease

# Platelet Adhesion




- Following activation, platelets undergo significant shape changes, producing elongated pseudopods that make the platelets extremely adhesive. Platelet adhesion is primarily mediated by the binding of platelet surface receptor GP Ib/IX/V complex to von Willebrand factor (VWF) in the subendothelial matrix. In addition, there are other adhesive interactions that contribute to platelet adhesion. One example is binding of the platelet collagen receptor GP Ia/IIa to collagen fibrils in the matrix

# Platelet aggregation

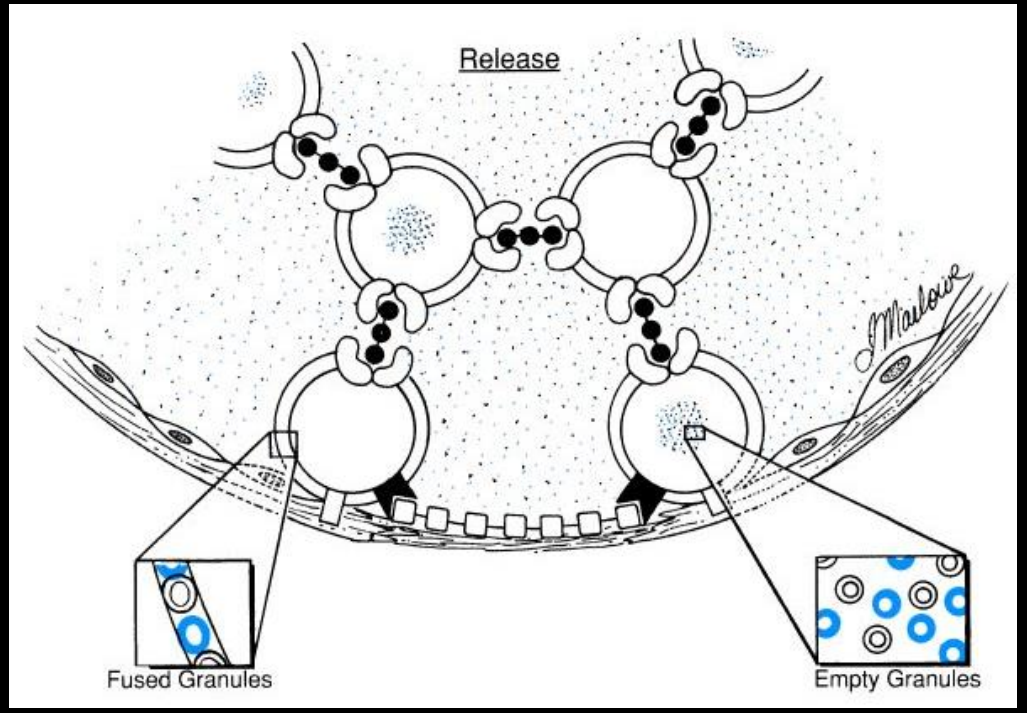



Platelet activation results in both exposure of and conformational changes in the GP IIb/IIIa receptor on the platelet surface, leading to binding of both immobilized VWF and fibrinogen . In addition to mediating platelet aggregation, the cytosolic portion of the activated GP IIb/IIIa complex binds to platelet cytoskeleton and can mediate platelet spreading and clot retraction, which has been referred to as "outside-in" integrin signaling. .

# Platelet secretion

Platelets secrete a variety of substances from their granules upon cell stimulation:

- ADP and serotonin
- Fibronectin and thrombospondin
- Fibrinogen
- Thromboxane A2
- Growth factors, such as platelet-derived growth factor (PDGF)



# Acquired disorders

- **Antiplatelet drugs**

  ***Aspirin***: Inhibition of cyclo-oxygenase with impaired thromboxane $A_2$ synthetasis so impairment of the release reaction and aggregation with adrenaline and adenosine diphophate(ADP).

  ***Dipridamol***: Inhibit plt. aggregation by bloking reuptake of adenosine

  ***Clopidogrel***: Inhibits binding of ADP to its platelet receptor

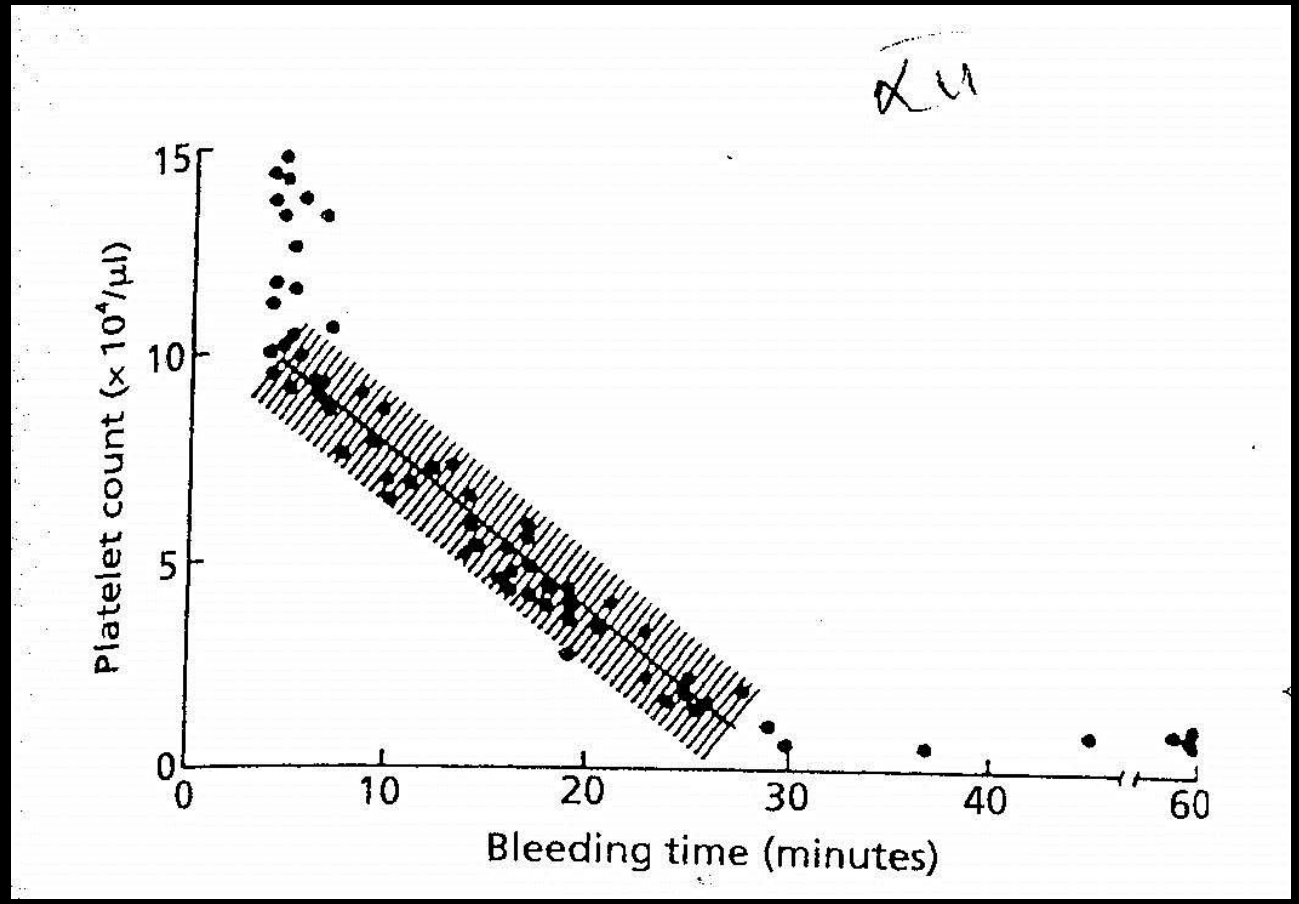
  ***Abciximab***: Inhibitors of GPIIb/IIIa

- **Hyperglobulinemia**: Interference with platelet adherence, release and aggregation

- **Myloproliferative and myelodysplasia**

- **Uremia**

# Prolongation of Bleeding Time in Thrombocytopenia



# Evaluation of Prolonged Bleeding Time in the Absence of Thrombocytopenia

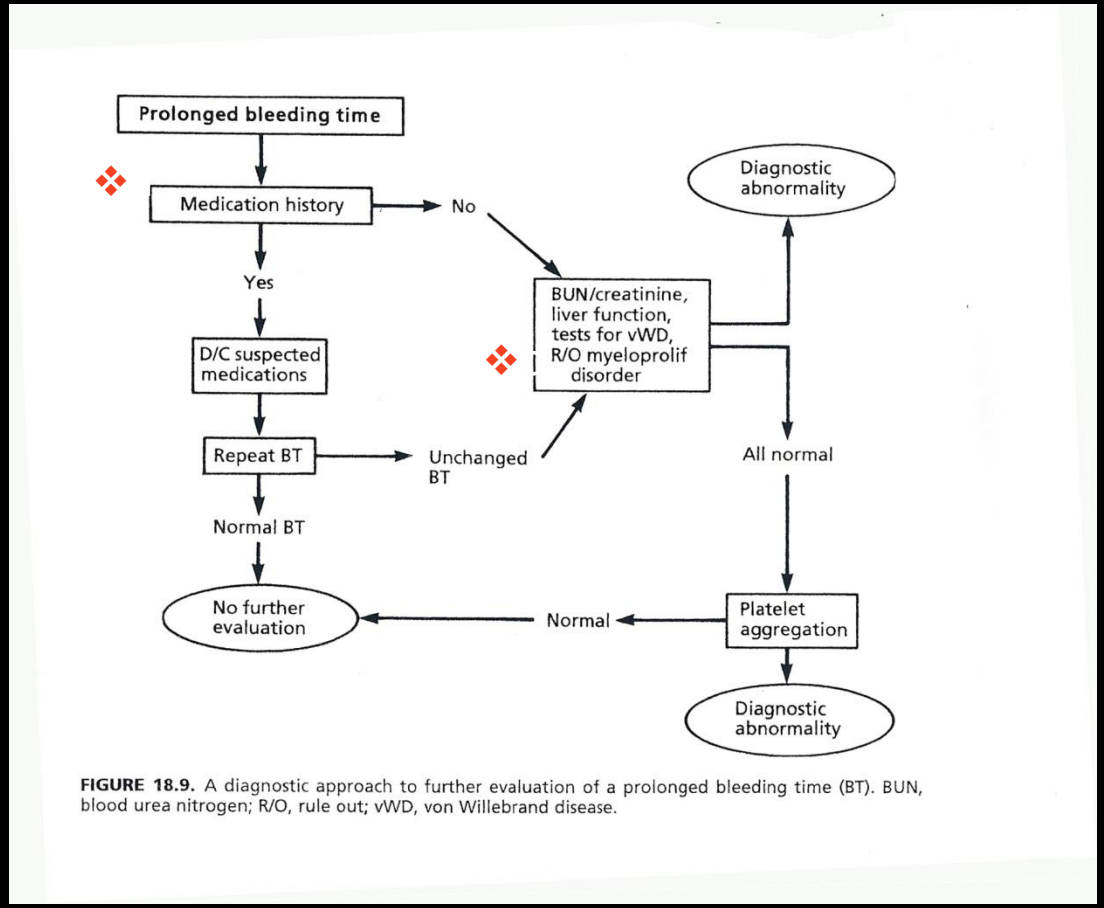
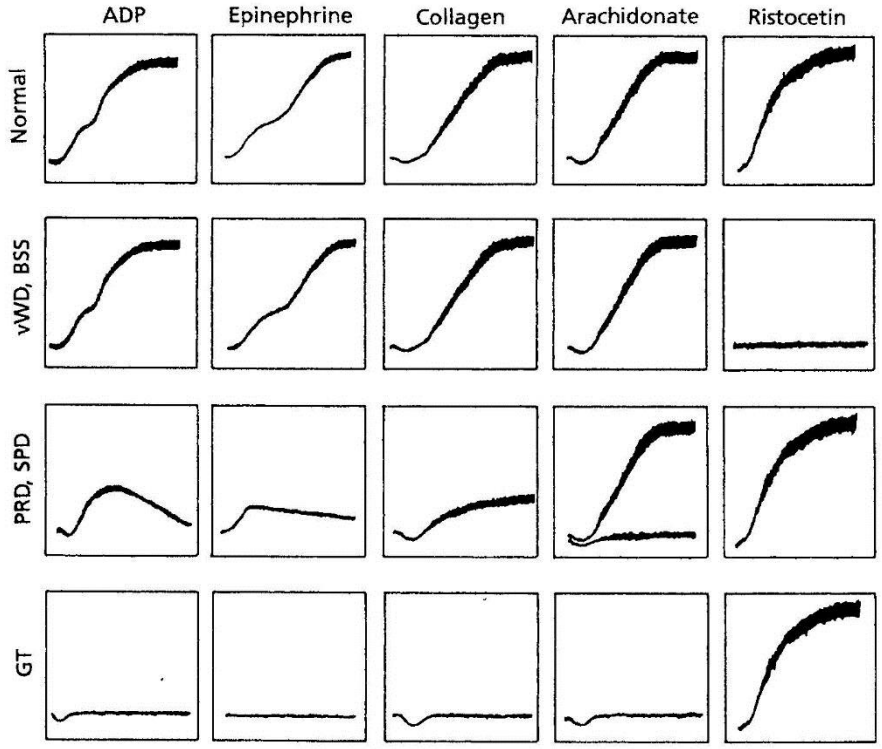



**FIGURE 18.9.** A diagnostic approach to further evaluation of a prolonged bleeding time (BT). BUN, blood urea nitrogen; R/O, rule out; vWD, von Willebrand disease.

# Platelet Aggregation Tests




Normal and abnormal pattern of platelet aggregation tests

# Coagulation disorders

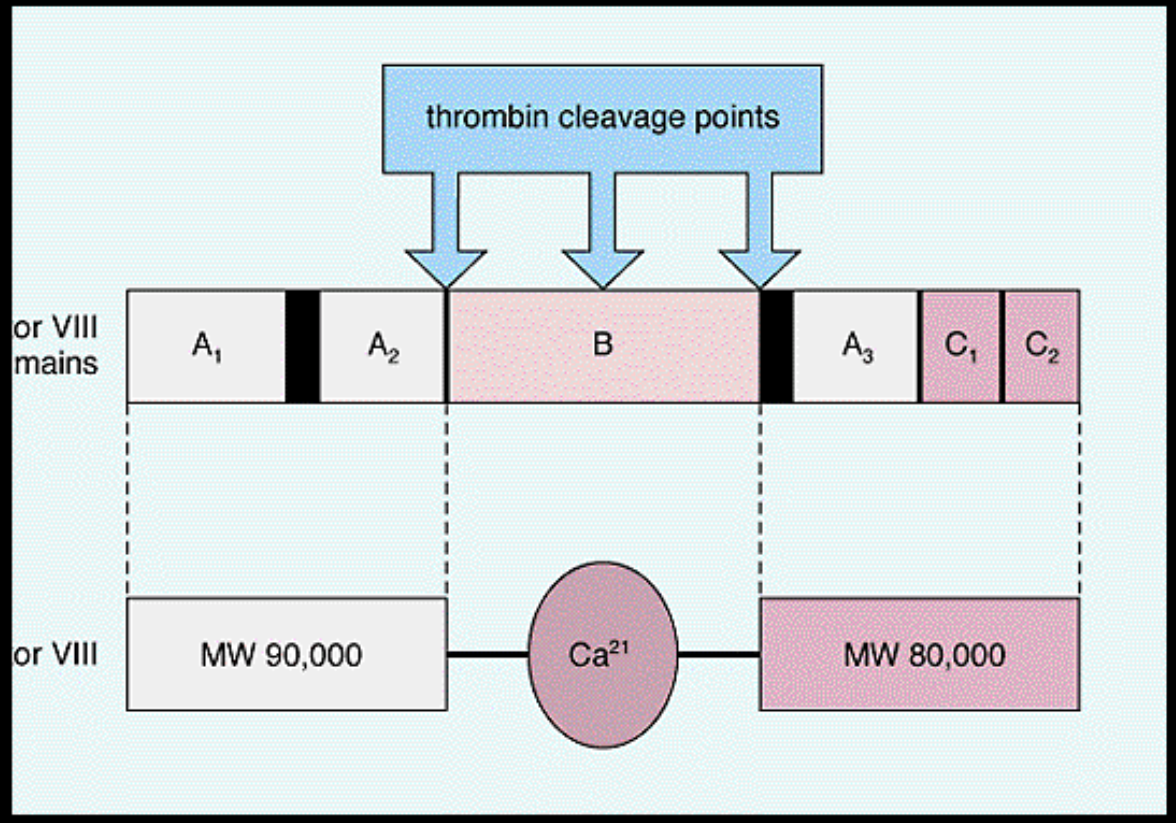
- HEREDITARY COAGULATION DIORDERS
- ACQUIRED COAGULATION DISORDERS

# HEREDITARY COAGULATION DIORDERS

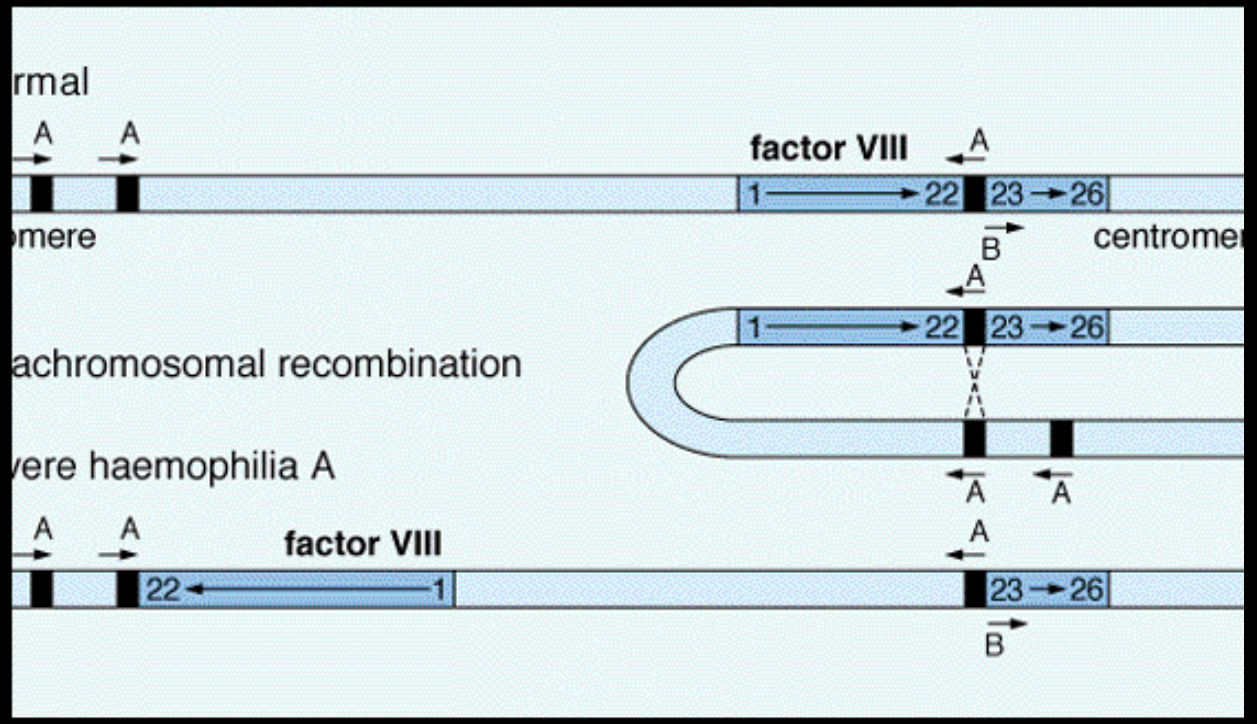
## Hemophilia A (factor VIII deficiency)

- The prevalence is of the order of 30-100 per million population.
- The inheritance is sex-linked but up to 33% of patients have no family history and result from spontaneous mutation.
- The factor VIII gene is situated near the tip of the long arm of the X chromosome. It is extremely large and consist of 26 exons
- The defect is an absence or low level of plasma factor VIII.
- Approximately half of the patients have missense of frame shift mutations or deletions in the factor VIII gene. In others a characteristic “flip-tip” inversion is seen, this mutation leads to a severe clinical form of hemophilia A.

# Factor VIII

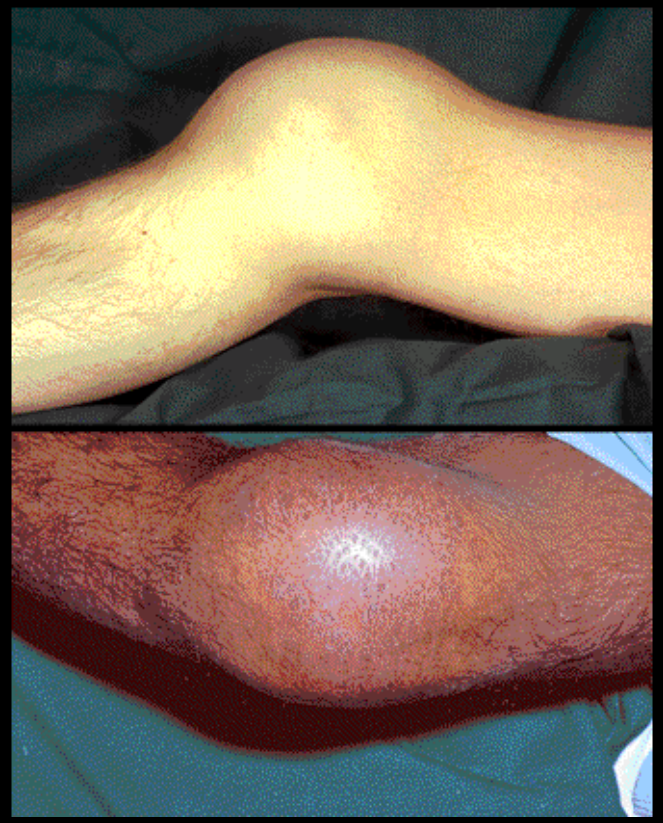

thrombin cleavage points
or VIII
mains
A1
A2
B
A3
C1
C2
or VIII
MW 90,000
Ca21
MW 80,000

# The mechanism of the flip-tip inversion



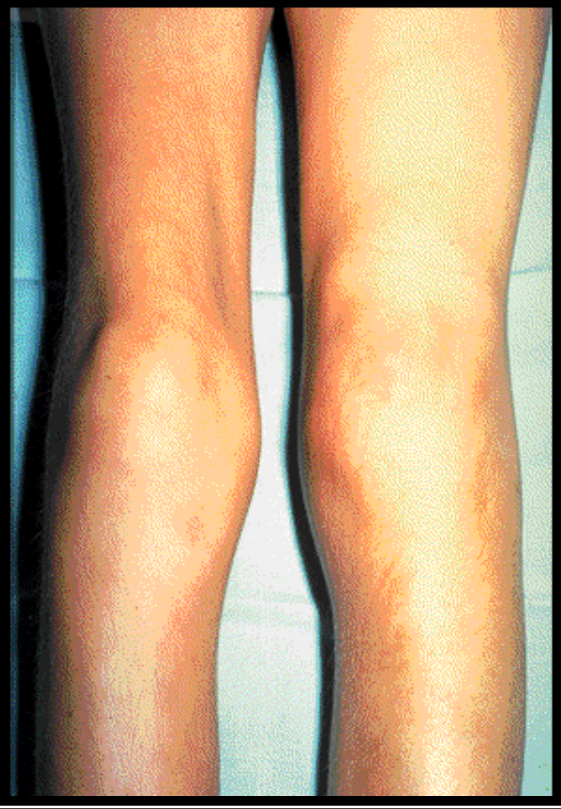
# Clinical feature

**Painful haemarthroses ,Muscle hematoma**



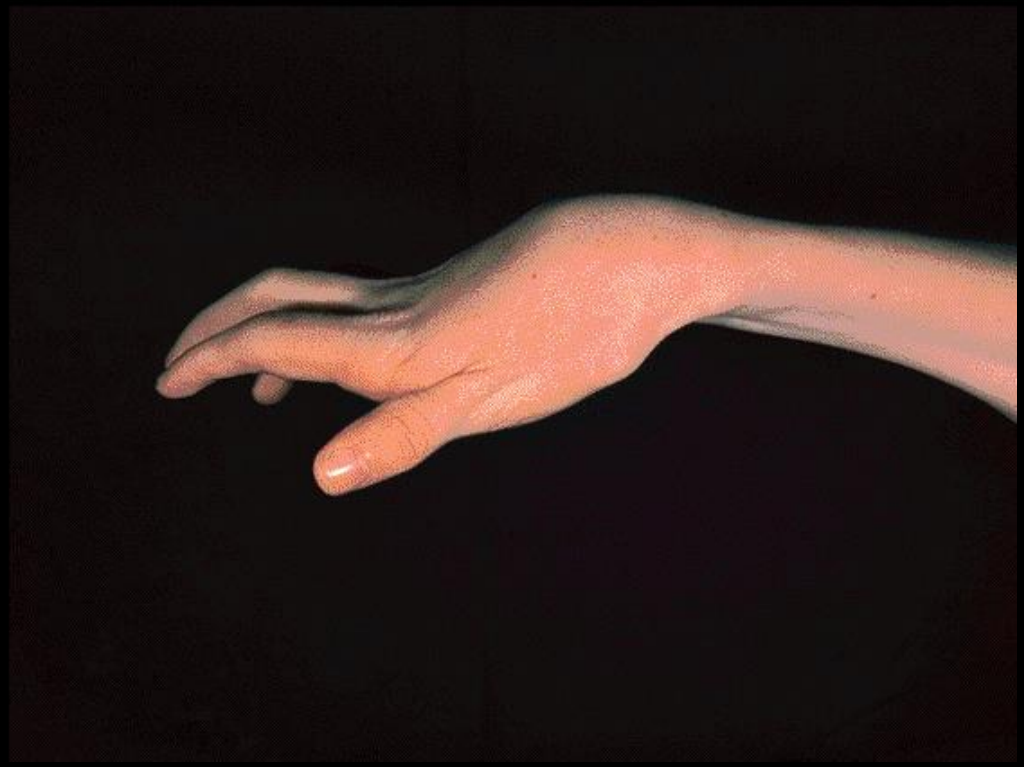
# Clinical feature

**Painful haemarthroses ,Muscle hematoma**



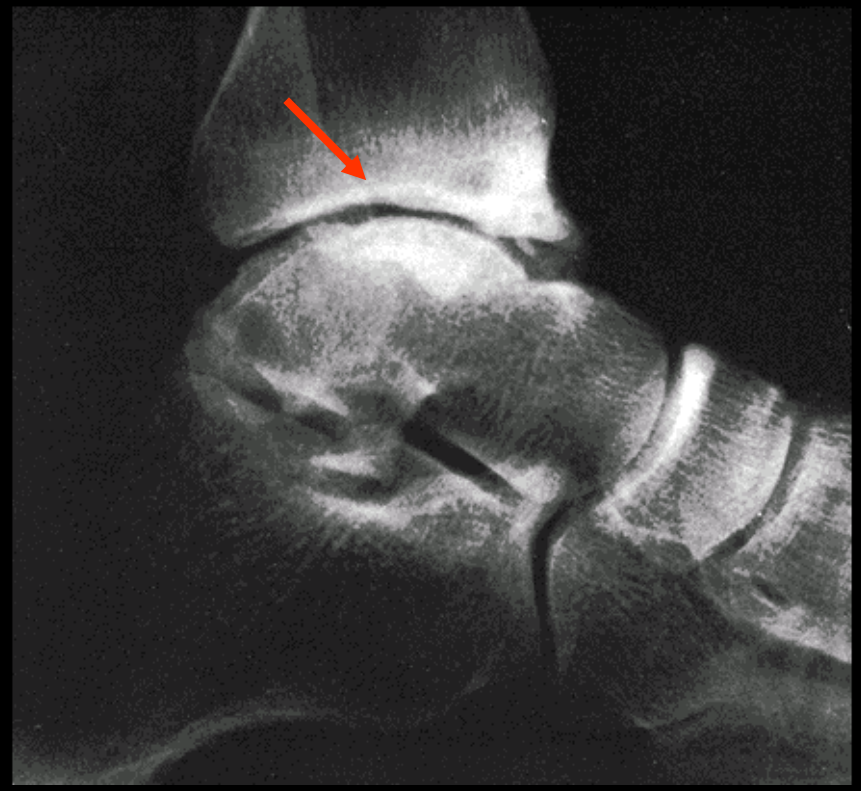
# Clinical feature

**Painful haemarthroses ,Muscle hematoma**



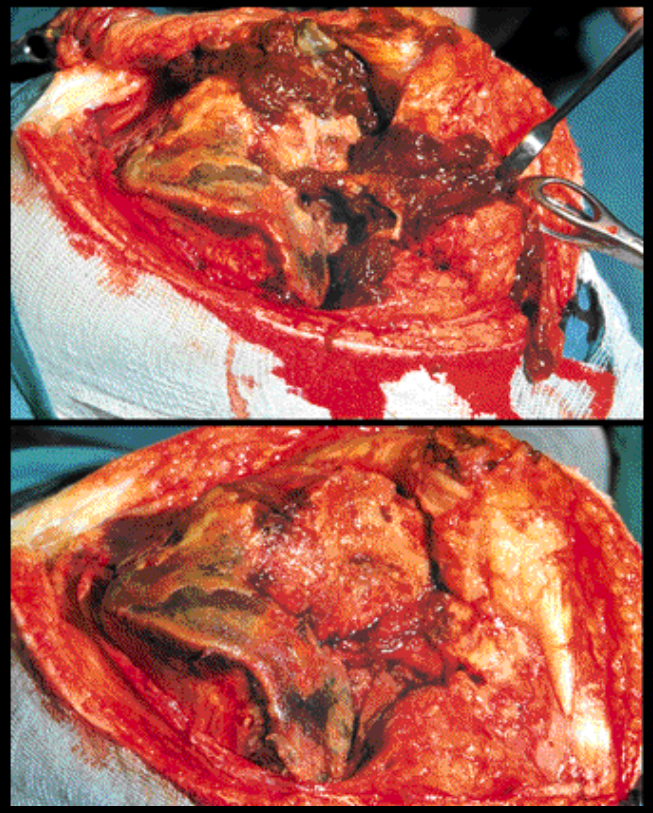
# Clinical feature

**Painful haemarthroses ,Muscle hematoma**



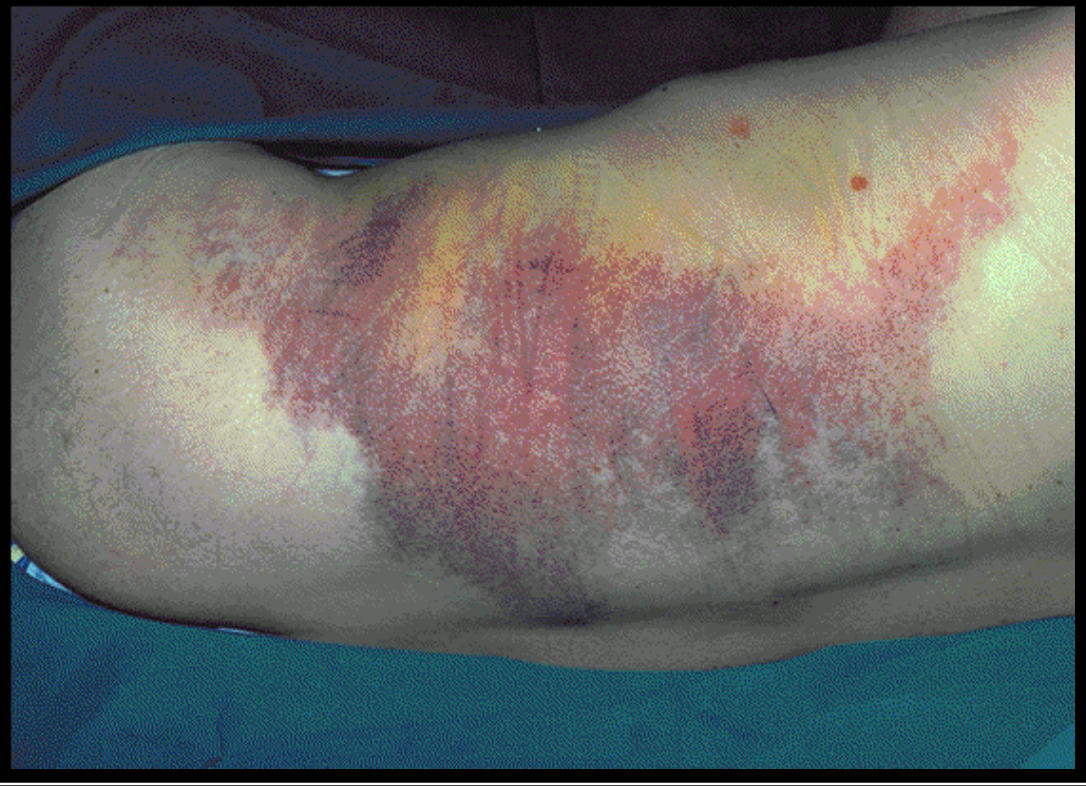
# Clinical feature

**Painful haemarthroses ,Muscle hematoma**



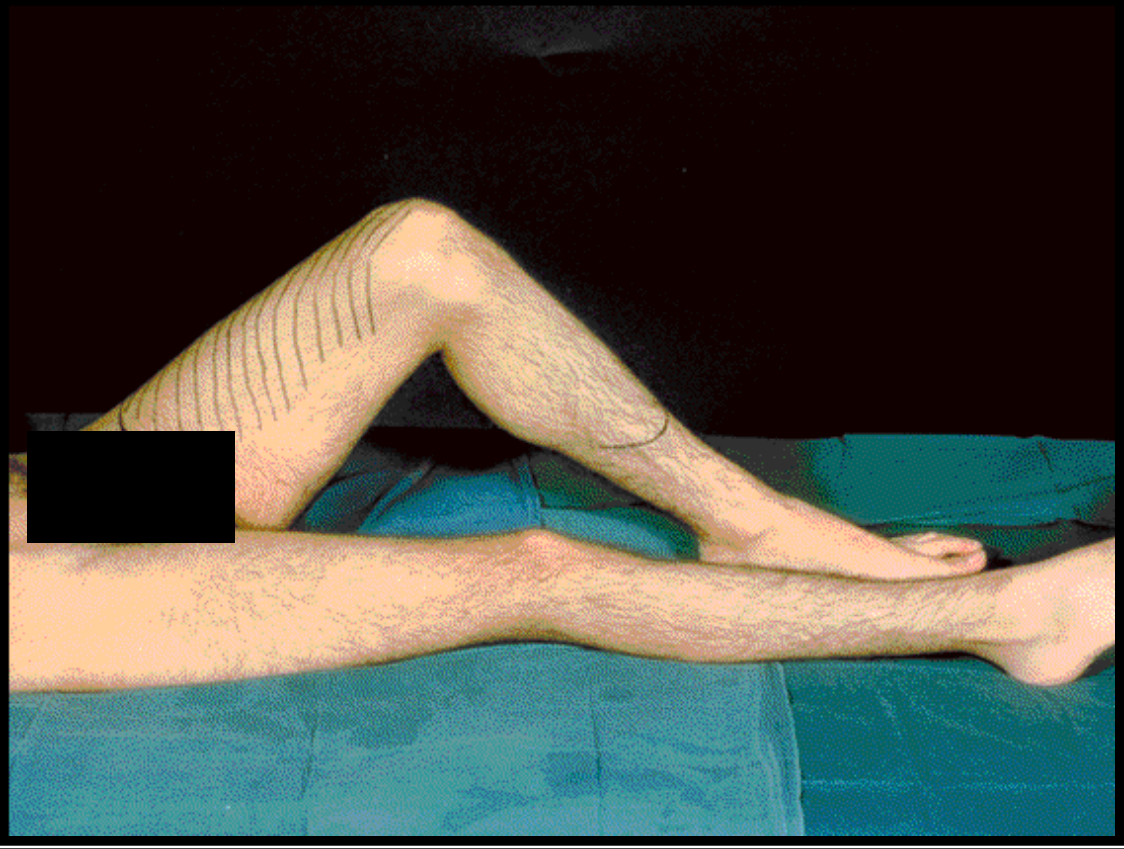
# Clinical feature

**Painful haemarthroses ,Muscle hematoma**



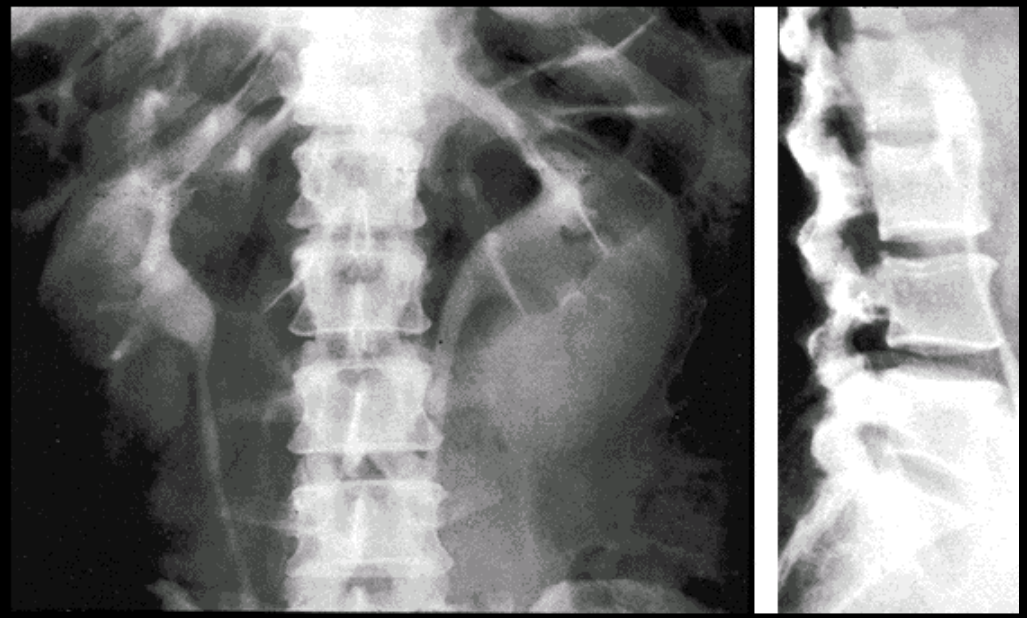
# Clinical feature

**Painful haemarthroses ,Muscle hematoma**



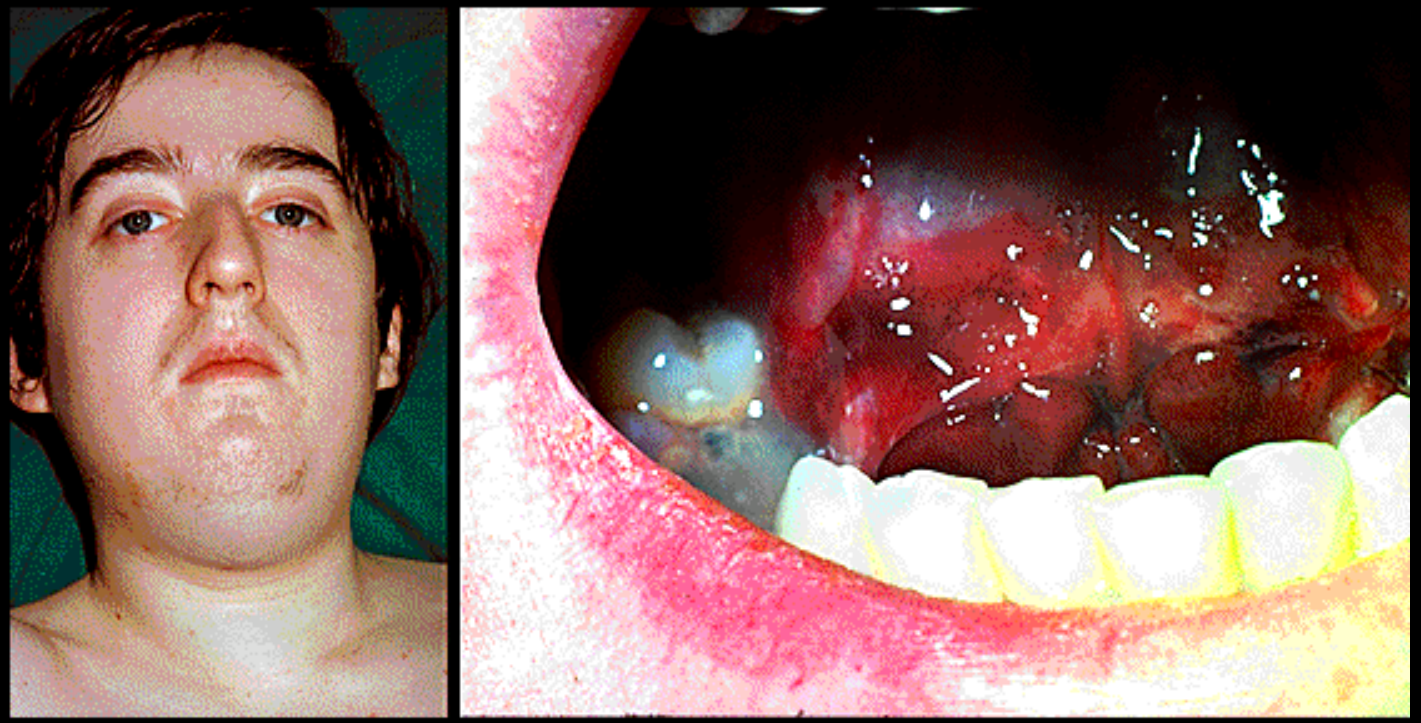
# Clinical feature

**Painful haemarthroses ,Muscle hematoma**



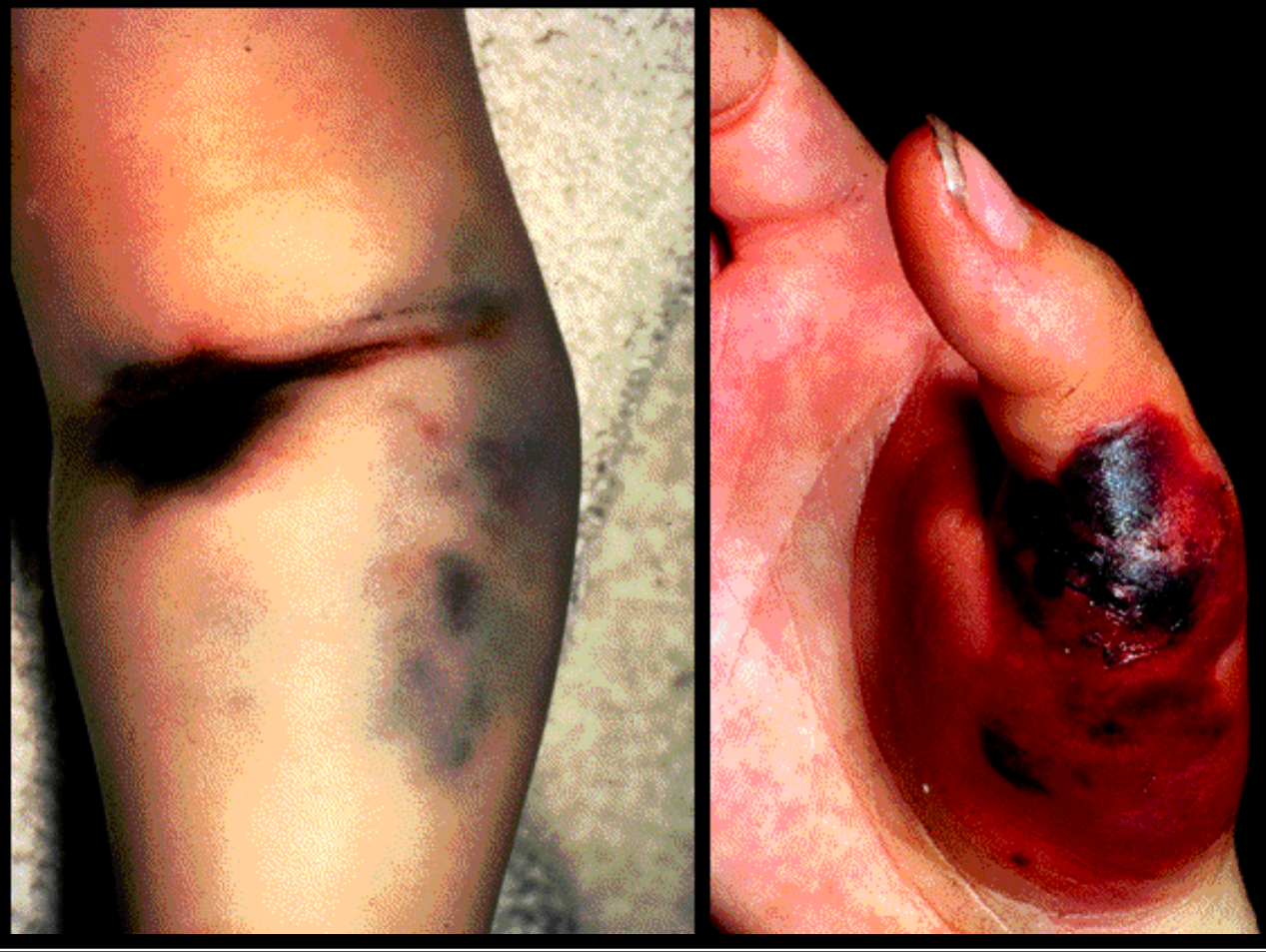
# Clinical feature

**Soft tissue  hematoma**



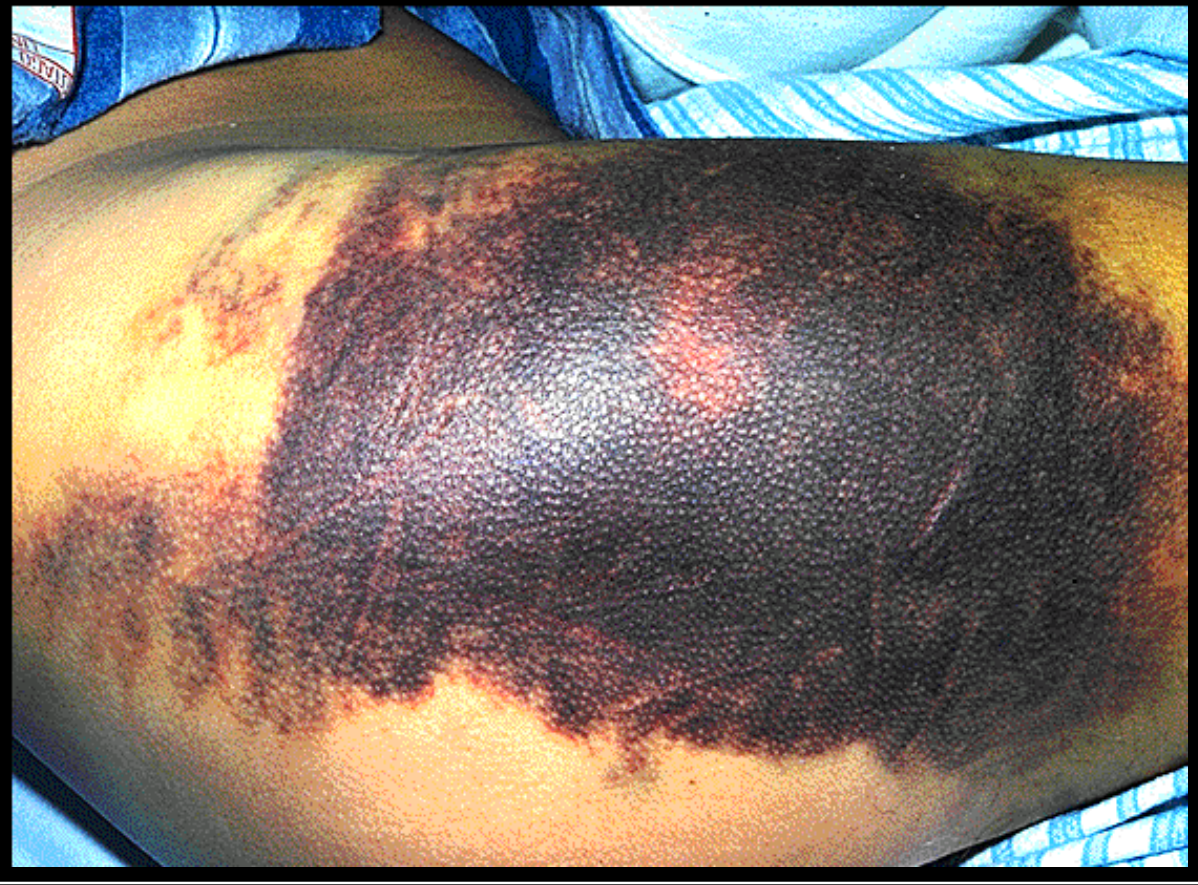
# Clinical feature

**Soft tissue  hematoma**



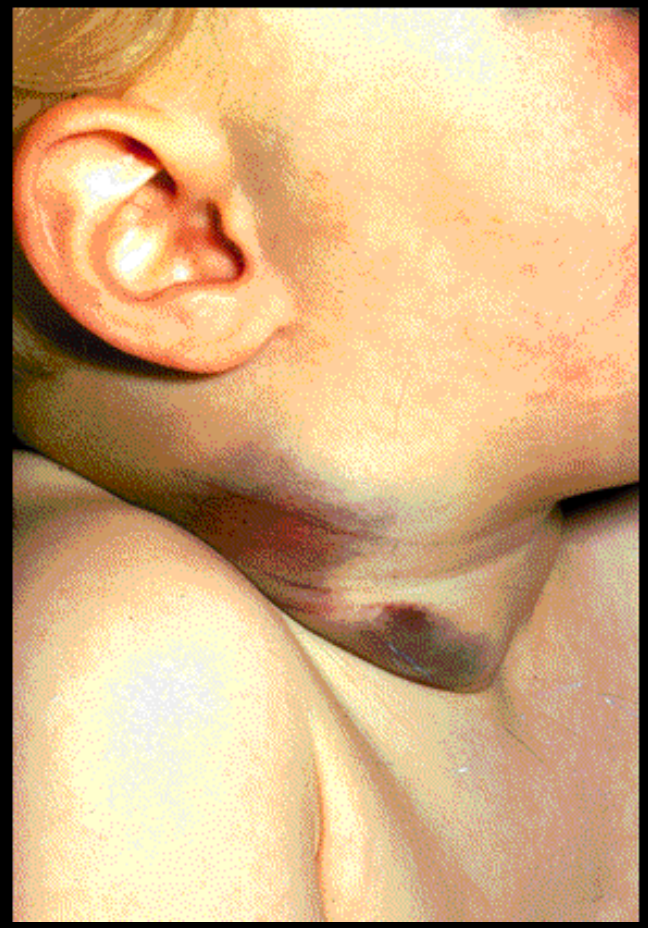
# Clinical feature

**Soft tissue  hematoma**



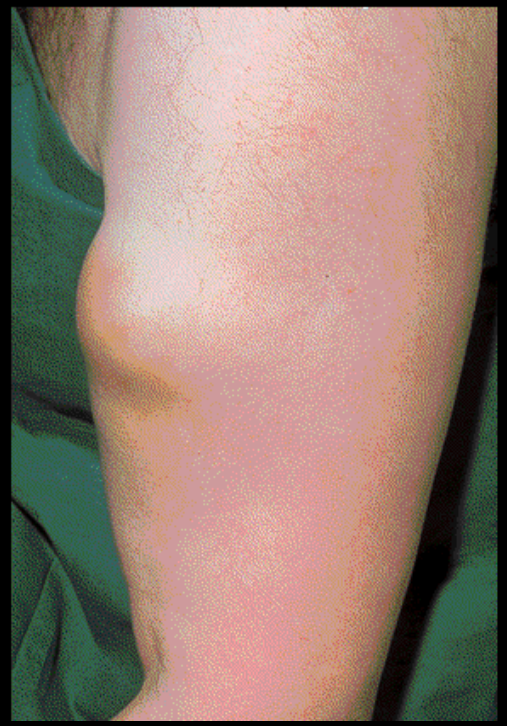
# Clinical feature

**Soft tissue  hematoma**



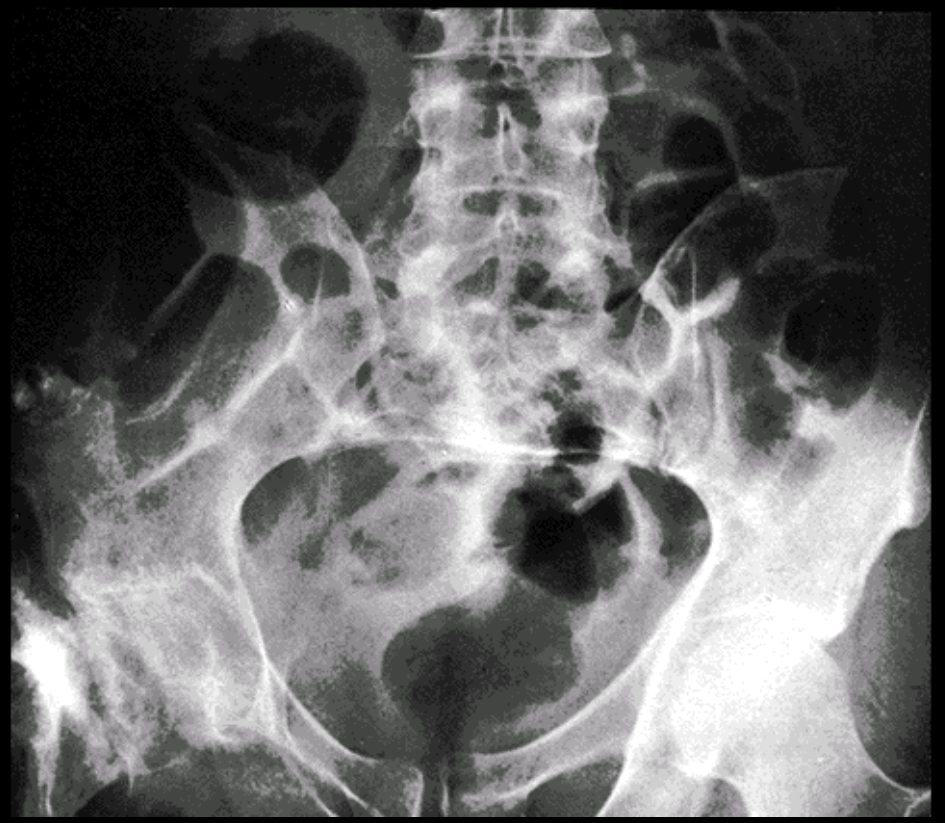
# Clinical feature

## Haemophilic pseudotumours



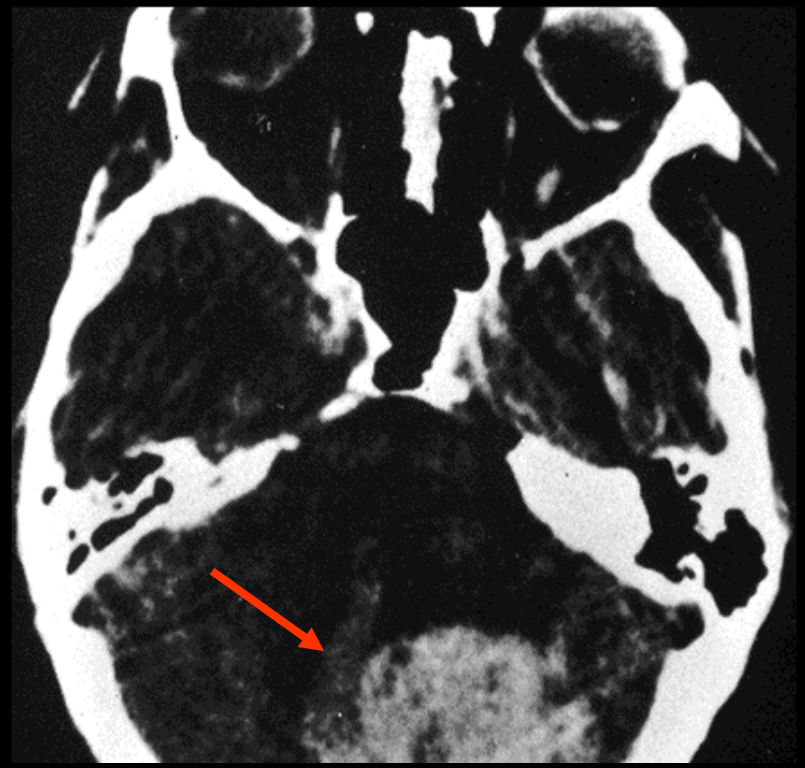
# Clinical feature

## Haemophilic pseudotumours



# Clinical feature

## Interacerbral hemorrhage



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

| Coagulation Factor activity (percentage of normal) | Clinical manifestation |
|---|---|
| <1 | Severe disease<br>Frequently spontaneous bleeding episodes from early life<br>Joint deformity and crippling if not adequately treated |
| 1-5 | Moderate disease<br>Post-traumatic bleeding<br>Occasional spontaneous episode |
| 5-20 | Mild disease<br>Post-traumatic bleeding |

# Laboratory findings

- The following tests are abnormal

  1-aPTT

  2-Factor VIII clotting assay

- The bleeding time and prothrombin time (PT) tests are normal.

# ***Carrier detection and antenatal diagnosis***

- Fetal DNA analysis:

  Chorionic biopsies at 8-10 weeks of gestation provide sufficient fetal DNA for analysis.

- Measuring plasma level of F:VIII and VWF:

  Fetal blood obtained at 16-20 weeks gestation from umblical vein by ultrasound-guided needle aspiration.

# Treatment

- Factor VIII replacement therapy
- DDAVP (desmopressin):

  An alternative means of increasing factor VIII level in milder haemophilia.
- Local supportive measures
- Prophylactic treatment
- Gene therapy

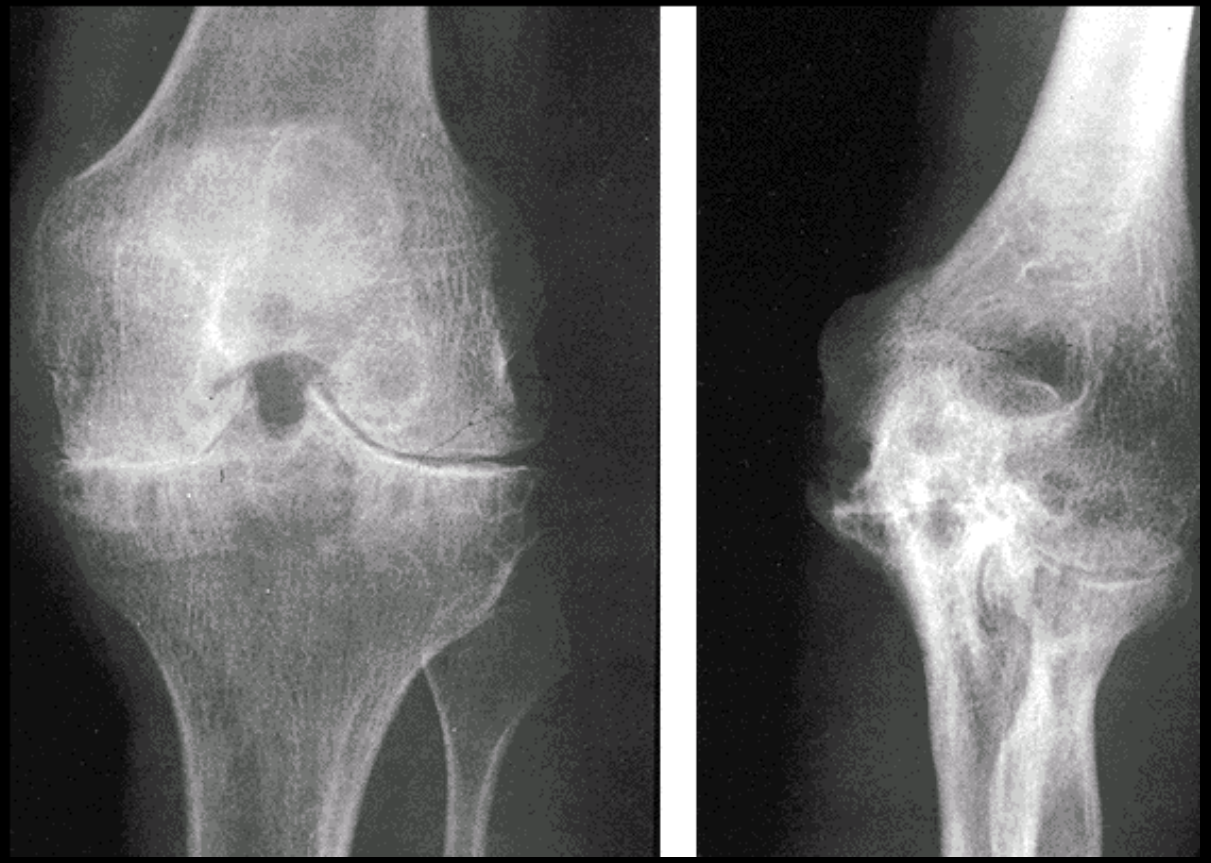
# ***Special complication***

- Transmitted infection:
  HIV infection (50%)
  HCV infection (many)

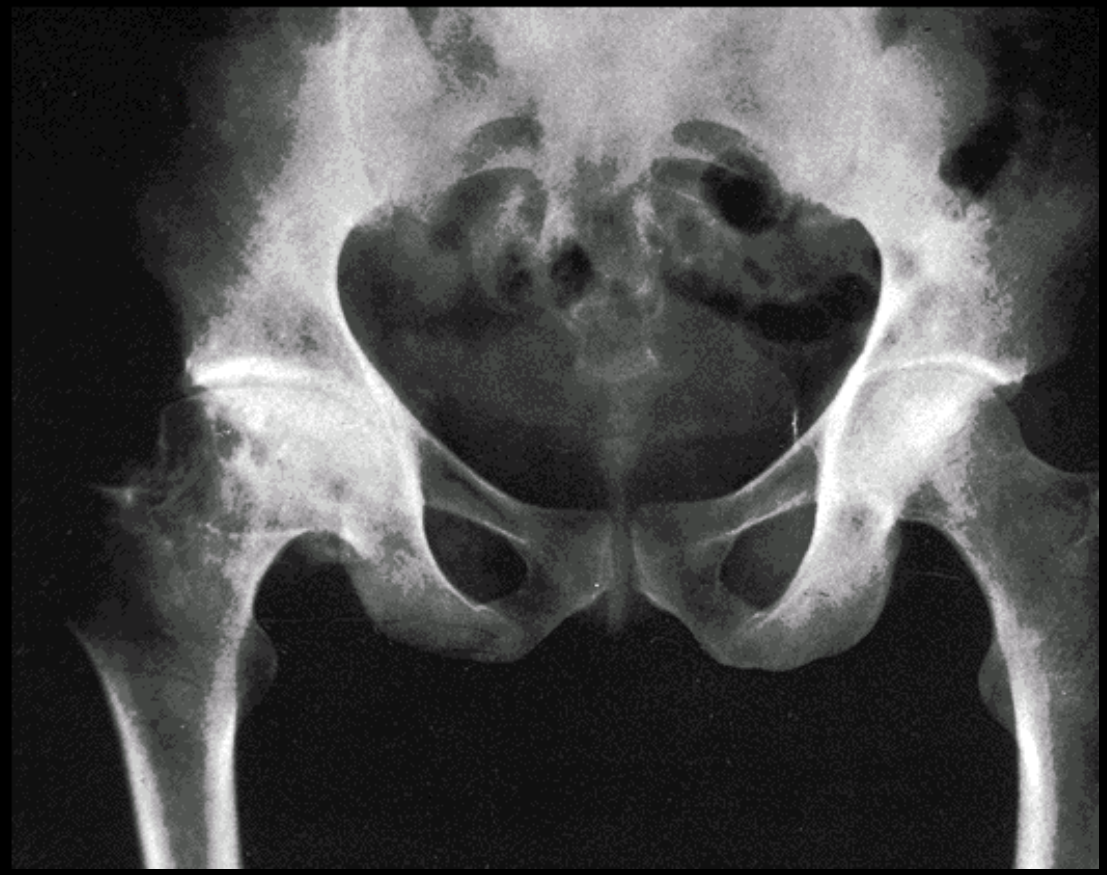
- Inhibitors: (5-10%)

- Joint deformity and disability

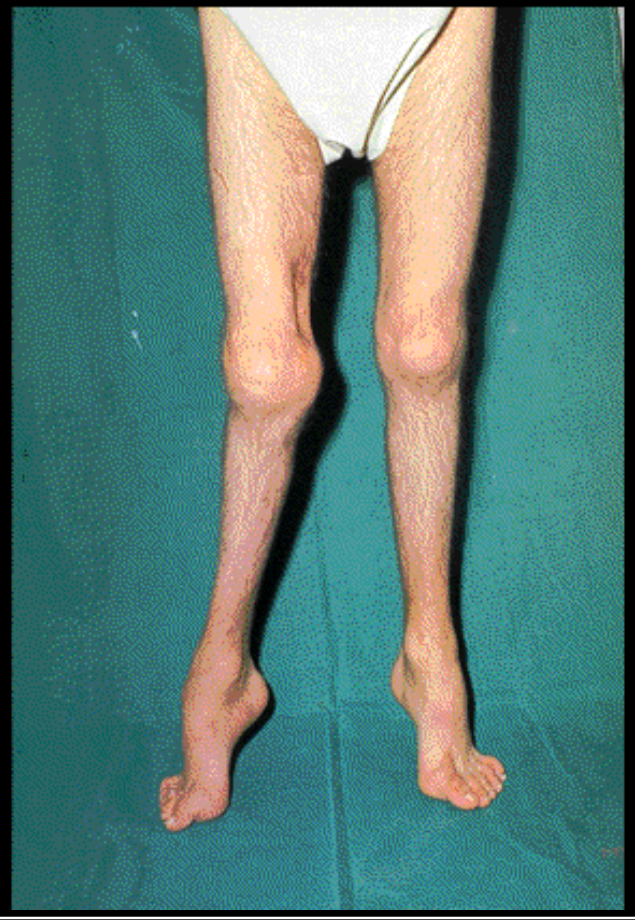
# Joint deformity and disability



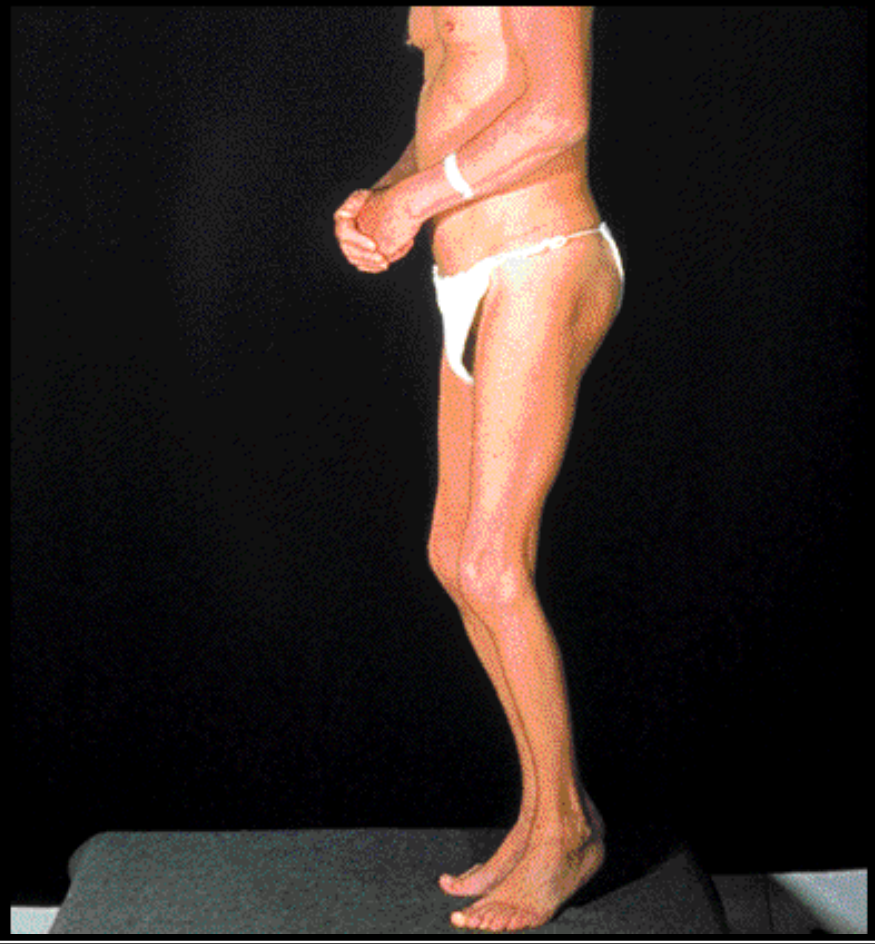
# Joint deformity and disability



# Joint deformity and disability



# Joint deformity and disability



# Factor IX deficiency

- The inheritance and clinical features of factor IX deficiency are identical to those of haemophilia A.
- The incidence is one-fifth that of haemophilia A.
- Factor IX is coded by a gene close to the gene for factor VIII near the tip of the X chromosme

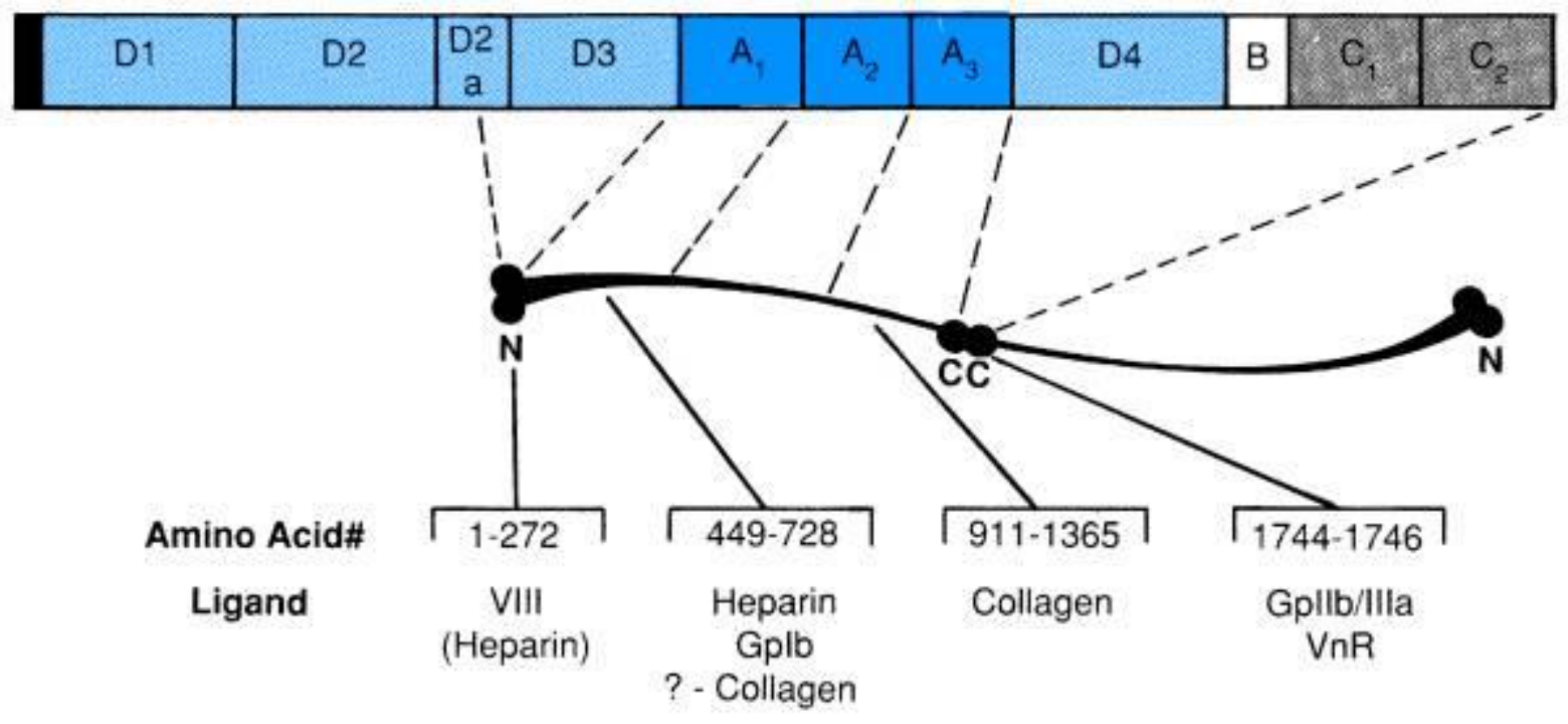
# INTRODUCTION

- von Willebrand's disease (vWD), the most common inherited coagulopathy (1% of general population), is best defined as a group of autosomally inherited bleeding disorders that are caused by quantitative or qualitative abnormalities in von Willebrand's factor (vWF).

- vWF has two roles in normal hemostasis. First, vWF provides a molecular bridge between platelets and the exposed subendothelium in damaged blood vessels. Second, vWF serves as an intravascular carrier for factor VIII, the procoagulant protein with which it is noncovalently complexed in the plasma, increasing the half-life of factor VIII five-fold, Thus, abnormalities in vWF may produce defects in primary and secondary hemostasis.

# Domain structure

Chr; 12p

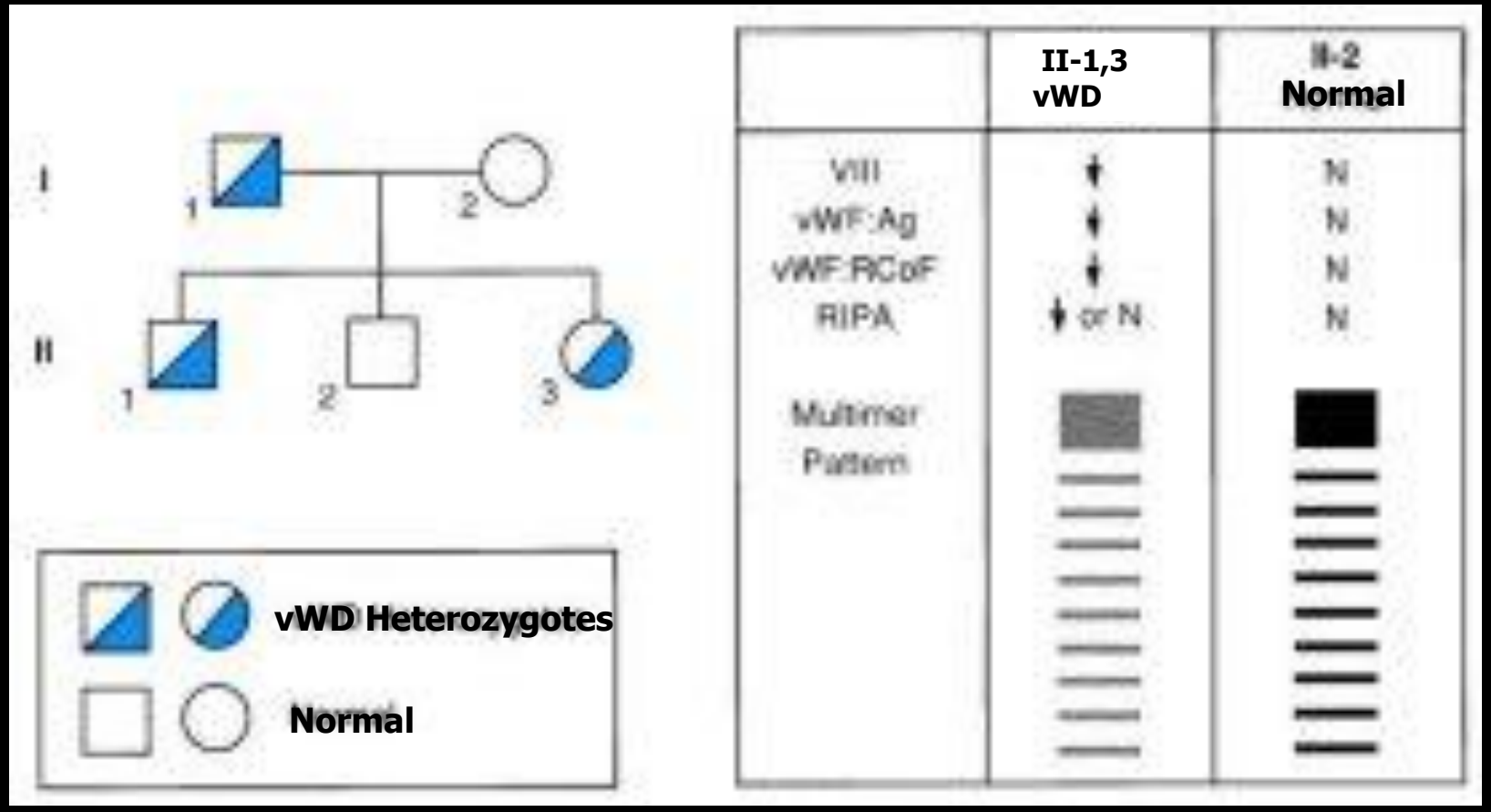


## Classification of Von Willebrand Disease

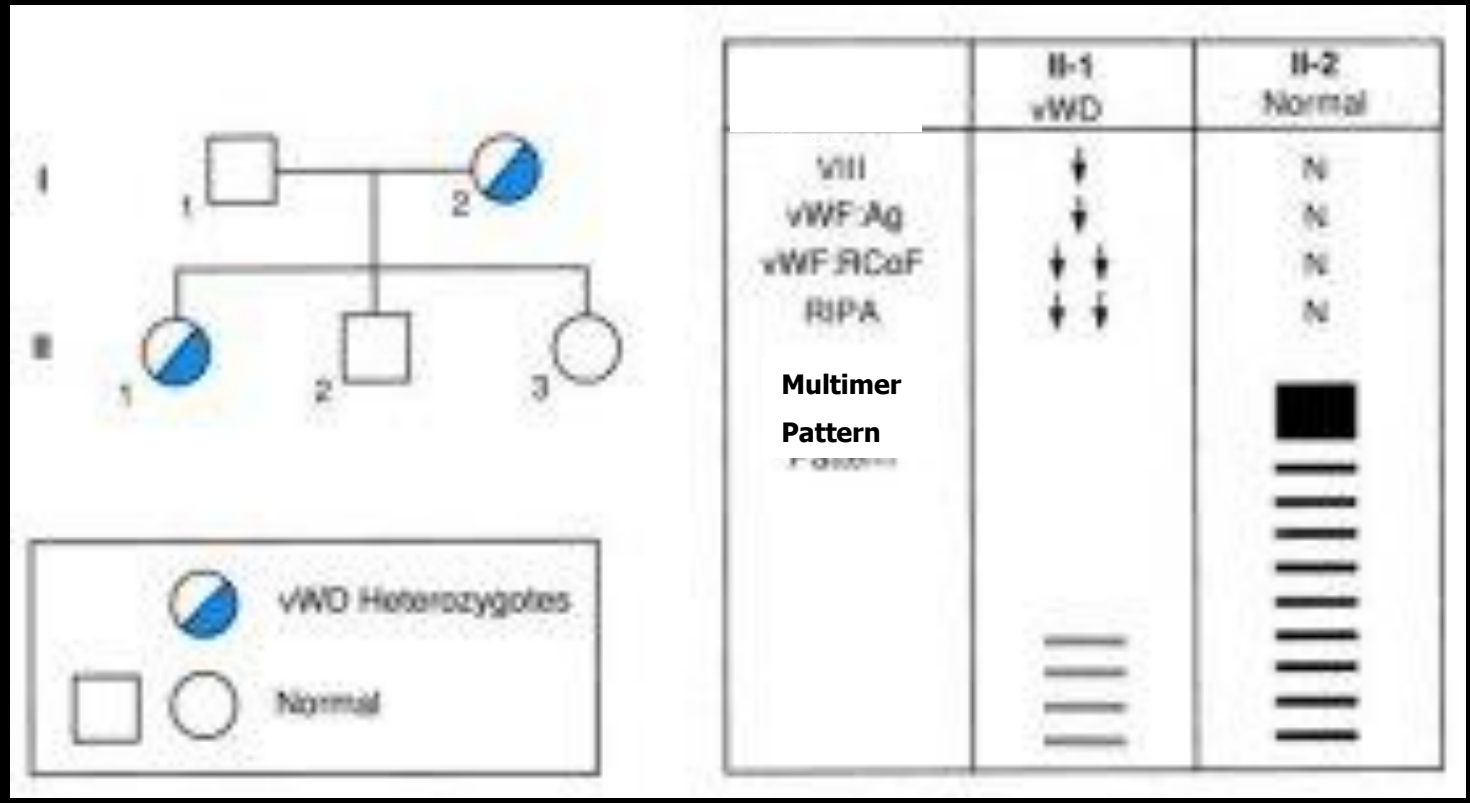
| Type | Inheritance | vWF activity† | RIPA* | Multimer pattern |
|---|---|---|---|---|
| 1 (classic) | Autosomal dominant | Decreased | Decreased | Uniform decrease; all multimers present |
| 2 (variant) | | | | |
| 2A | Autosomal dominant or recessive | Decreased | Decreased | Decreased large and intermediate multimers |
| 2B | Autosomal dominant | Decreased | Increased | Decreased large multimers |
| 2M | Autosomal dominant | Decreased | Decreased | Normal multimers |
| 2N | Autosomal recessive | Normal | Normal | Normal multimers |
| 3 (severe) | Autosomal recessive | Markedly decreased | Markedly decreased | Undetectable; usually cannot visualize |

† vWF activity = ristocetin cofactor activity
* RIPA = Ristocetin-induced platelet aggregation

# Von Williberand type I



# Von Williberand type IIA



# Type 2B

- Type 2B VWD accounts for approximately 5 percent of cases of VWD, and is transmitted as an autosomal dominant trait. Affected patients generally present with moderate or moderately severe bleeding.

- Mutations causing type 2B disease occur within a 38-amino acid sequence and account for the majority of patients with this disease variant. These mutations appear to disrupt the structure within the A1 domain that contains the binding site for platelet GP 1b, and result in a VWF that binds more readily to GP Ib ;thus it represents a "gain-of-function" mutation.
- The increase in binding of larger VWF multimers to platelet GP Ib results in their loss from the circulation and, in some patients, thrombocytopenia that is apparently due to clearance of the small platelet aggregates that are formed .Similar phenotypic abnormalities can be produced by mutations in GP Ib that cause it to bind more avidly to normal VWF; this disorder is called platelet-type or pseudo VWD

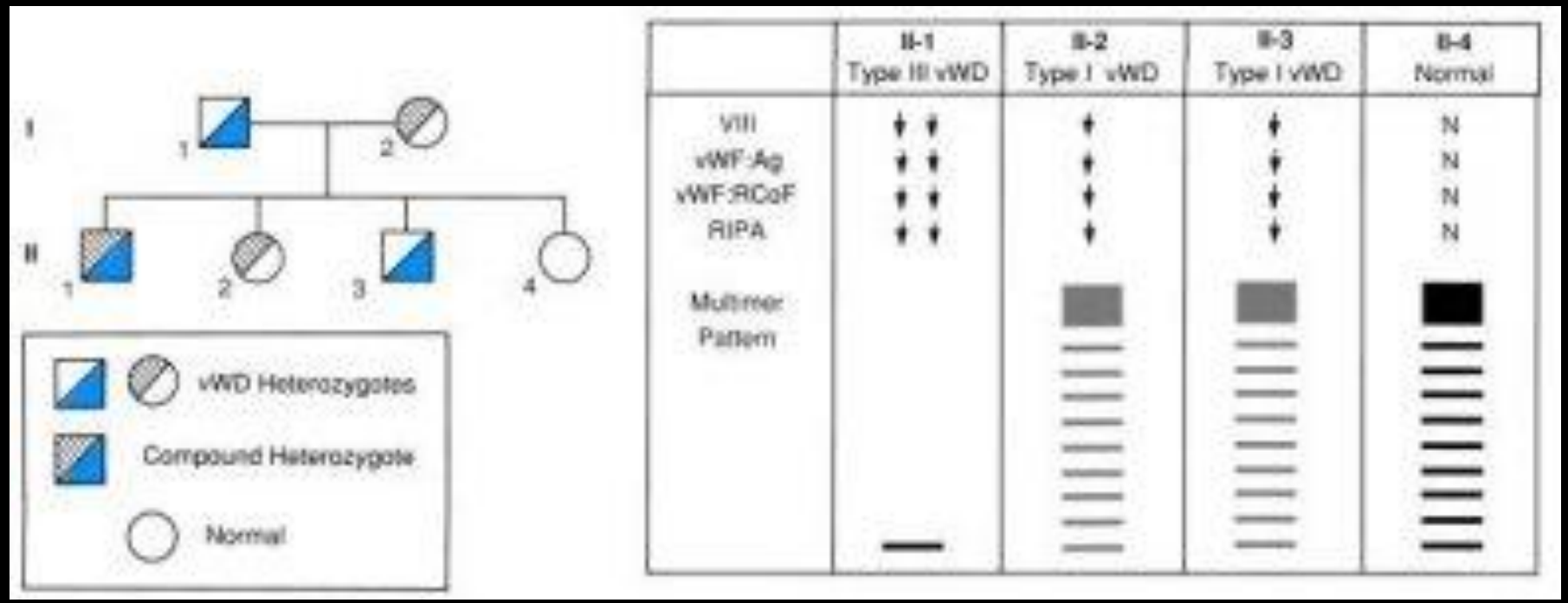
# Type 2M

- Type 2M VWD is a rare, autosomal dominant disorder characterized by reduced binding of VWF to GP Ib.
- Mutations are located in the A1 loop of VWF in a different region from the mutations that cause type 2B VWD
- Affected patients typically have significant bleeding symptoms.

# Type 2N

- Type 2N VWD (N is for Normandy where one of the first patients was described) is an uncommon disorder that is inherited as an autosomal recessive trait. Most mutations affect the N-terminus of the mature VWF monomer within the binding site for factor VIII, causing decreased binding to factor VIII .The mutations primarily occur in the D' and D3 domains ,and are distributed in several areas throughout the first 91 amino acids.
- Affected patients present with low levels of factor VIII (usually 5 to 15 percent of normal) due to proteolytic cleavage of factor VIII that is normally impeded by the binding of factor VIII to VWF .In comparison to other forms of VWD, the platelet-related functions of VWF are not affected and VWF antigen and multimer patterns are normal.

# Von Williberand type III




| | II-1 Type III vWD | II-2 Type I vWD | II-3 Type I vWD | II-4 Normal |
|---|---|---|---|---|
| VIII | ↓ ↓ | ↓ | ↓ | N |
| vWF:Ag | ↓ ↓ | ↓ | ↓ | N |
| vWF:RCoF | ↓ ↓ | ↓ | ↓ | N |
| RIPA | ↓ ↓ | ↓ | ↓ | N |
| Multimer Pattern | — | ▬ + ═ | ▬ + ═ | ▬ + ═ |

# TREATMENT OF INHERITED VWD

There are five classes of specific medications for the treatment of VWD:

- Desmopressin;
- Replacement therapy with VWF-containing concentrates;
- Antifibrinolytic drugs;
- Topical therapy with thrombin or fibrin sealant
- Estrogen therapy in some settings in women .

☞ Several reports also indicate a role for factor VIIa in the treatment of patients with severe (type 3) VWD who develop inhibitors to replacement VWF

# ACQUIRED COAGULATION DISORDER

## Acquired Coagulation Disorders

Liver disease

Deficiency of vitamin K-dependent factors:
- haemorrhagic disease of the newborn;
- biliary obstruction;
- malabsorption of vitamin K, e.g. sprue, coeliac disease;
- vitamin K-antagonist therapy, e.g. coumarins, indanediones

Disseminated intravascular coagulation

Inhibition of coagulation:
- specific inhibitors, e.g. antibodies against factor VIII components;
- non-specific inhibitors, e.g. antibodies found in systemic lupus erythema
  rheumatoid arthritis

Miscellaneous:
- diseases with M-protein production;
- L-asparaginase;
- therapy with heparin, defibrinating agents or thrombolytics;
- massive transfusion syndrome

## Conditions Associated with Disseminated Intravascular Coagulation

**Infections**
- Gram-negative & meningococcal septicaemia
- septic abortion & *Clostridium welchii* septicaemia
- severe falciparum malaria
- viral infection (purpura fulminans)

**Malignancy**
- widespread mucin-secreting adenocarcinoma
- acute promyelocytic leukaemia

**Obstetric complications**
- amniotic fluid embolism

**Hypersensitivity reactions**
- anaphylaxis
- incompatible blood trans

**Widespread tissue damage**
- following surgery or traun

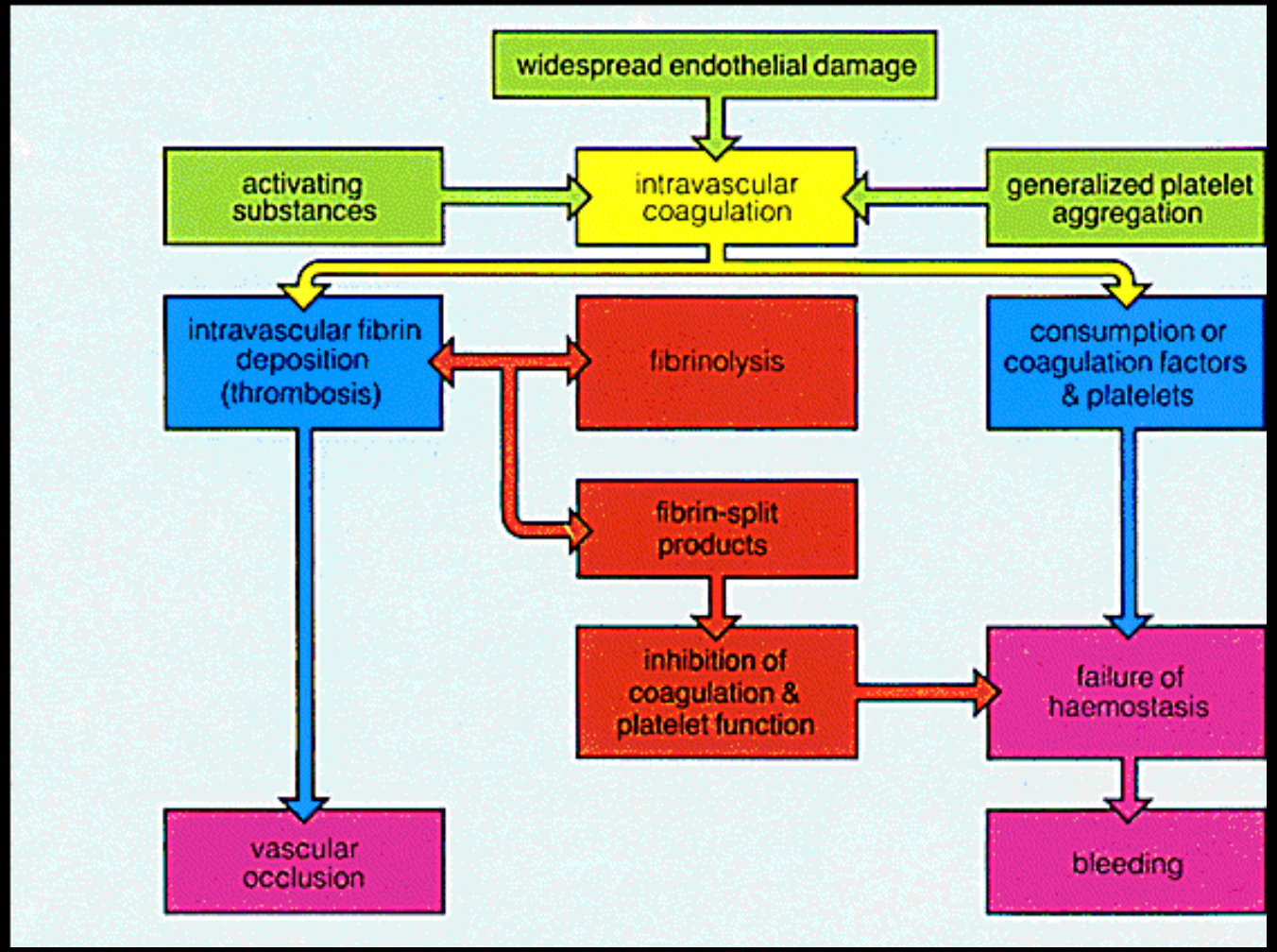
**Miscellaneous**
- liver failure
- snake & invertebrate ven
- severe burns
- hypothermia
- heat stroke
- hypoxia

# Pathogenesis

- DIC may be triggered by the entry of procoagulant material into the circulation in the following situation: amniotic fluid embolism, premature separation of the placenta,wide spread mucine-secreting adenocarcinomas, $AML_3$, liver disease ,severe falciparum malaria, hemolytic transfusion reaction and some snake bites.

- DIC may also be initiated by widespread endothelial damage and collagen exposure( endotoxinemia, Gram-negative and meningococcal septicemia, septic abortion), severe burns or hypothermia certain virus infection.

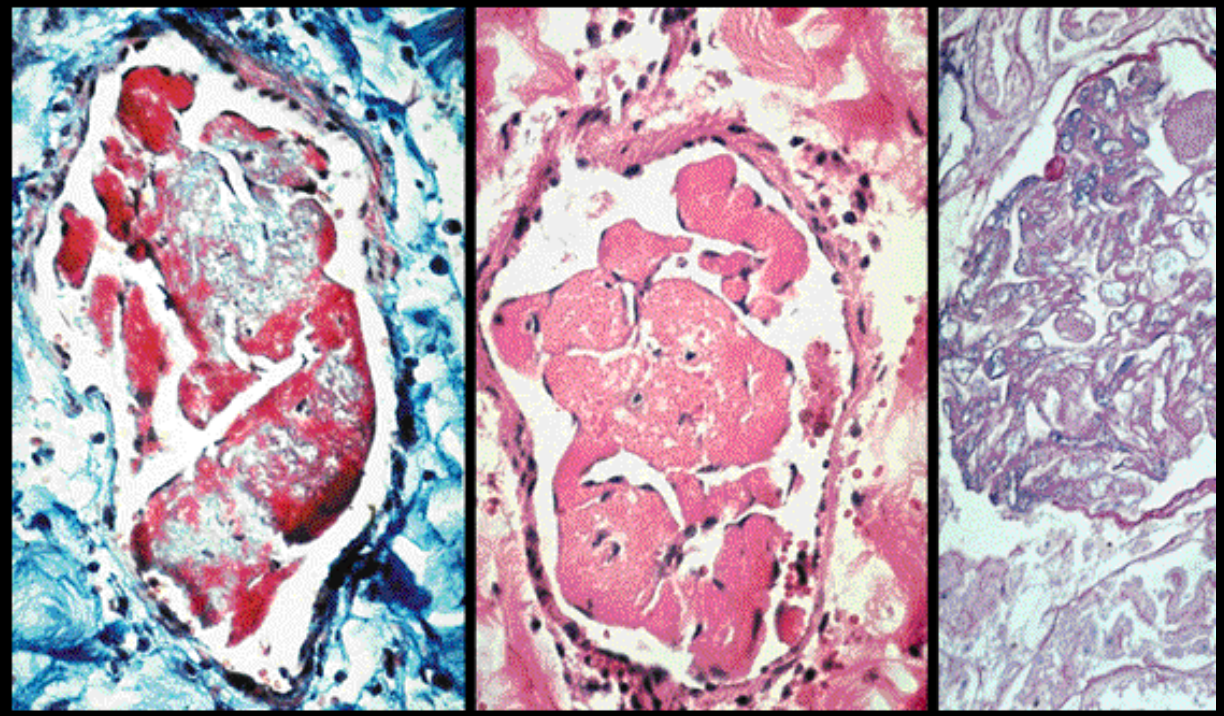
# Pathogenesis



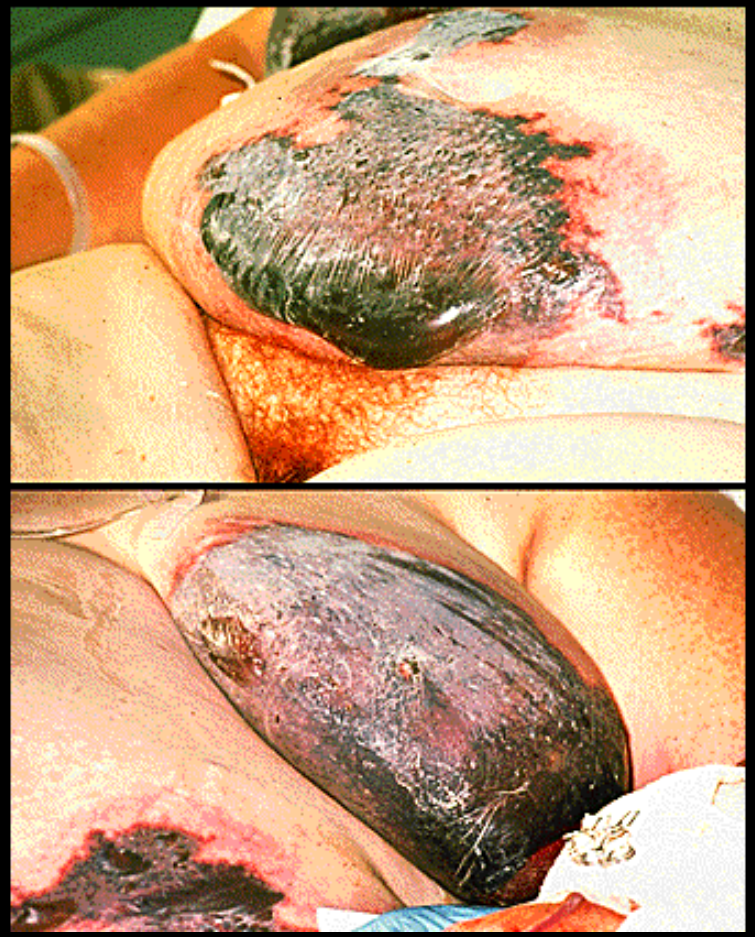
# Pathology

Skin

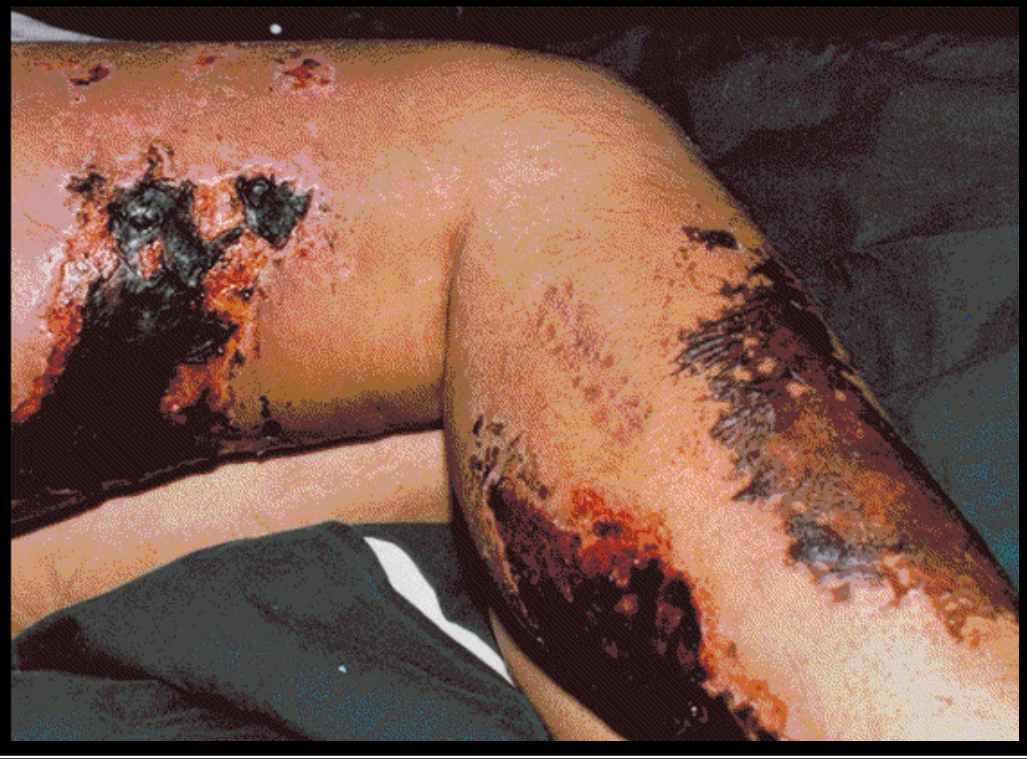
Glumerol



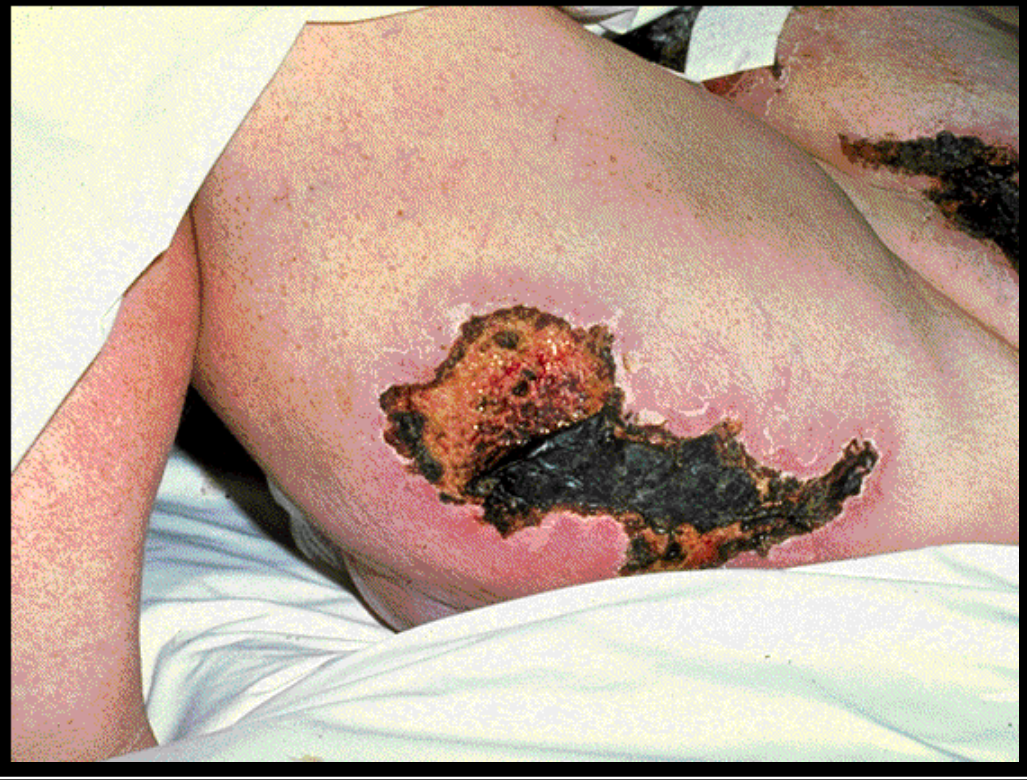
# Clinical Features



# Clinical Features



# Clinical Features



# Laboratory findings

***Tests of haemostasis***

1.The platelet count is low

2.Fibrinogen screening tests, titers or assays indicate deficiency.

3.The thrombin time is prolonged

4.High levels of fibrinogen (and fibrin) degradation products such as D-dimers are found in serum and urine

5. The PT and APTT are prolonged in the acute syndromes

***Blood film examination***

Red cells show prominent fragmentation (microangiopatthic

# Treatment

- Treatment of the underlying cause is the most important.
- Supportive therapy with fresh frozen plasma or cryoprecipitate and platelet concentrates is indicated in patients with dangerous or extensive bleeding.
- The use of antithrombin and protein C concenterates to inhibit DIC in severa cases appears promising.
- The use of heparin or antiplatelet drugs is usually not indicated because bleeding may be aggravated.
- Fibrinolytic inhibitors should not be consideredbecause failure to lyse thrombiin organs such as kidney may have adverse effect.