BLEEDING DISORDERS

BY:

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LEARNING OBJECTIVES

- To know the main sequence of events in the coagulation pathways
- To know the principles underlying the prothrombin time (PT), activated partial thromboplastin time (APTT) and thrombin time (TT)
- To know the principles of investigation of a patient suspected of having a haemostatic defect

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- To know the mode of inheritance, clinical presentation, method of diagnosis and principles of treatment of haemophilia A (factor FVIII deficiency), haemophilia B (factor IX deficiency), haemophilia C (factor XI deficiency) and von Willebrand disease (VWD)
- To know the alterations in the haemostatic and fibrinolytic mechanisms associated with disseminated intravascular coagulation (DIC) and the causes of DIC
- To understand normal fibrinolysis and the principles of fibrinolytic therapy

cont'd…

- To understand the principles of anticoagulant therapy with unfractionated heparin, low molecular weight heparin and warfarin and to know about the laboratory control of such therapy
- To be aware of the natural anticoagulant mechanisms in blood and some of the prothrombotic states (thrombophilia)
- To know the effects of vitamin K deficiency and liver disease on the clotting mechanisms

Normal Haemostasis

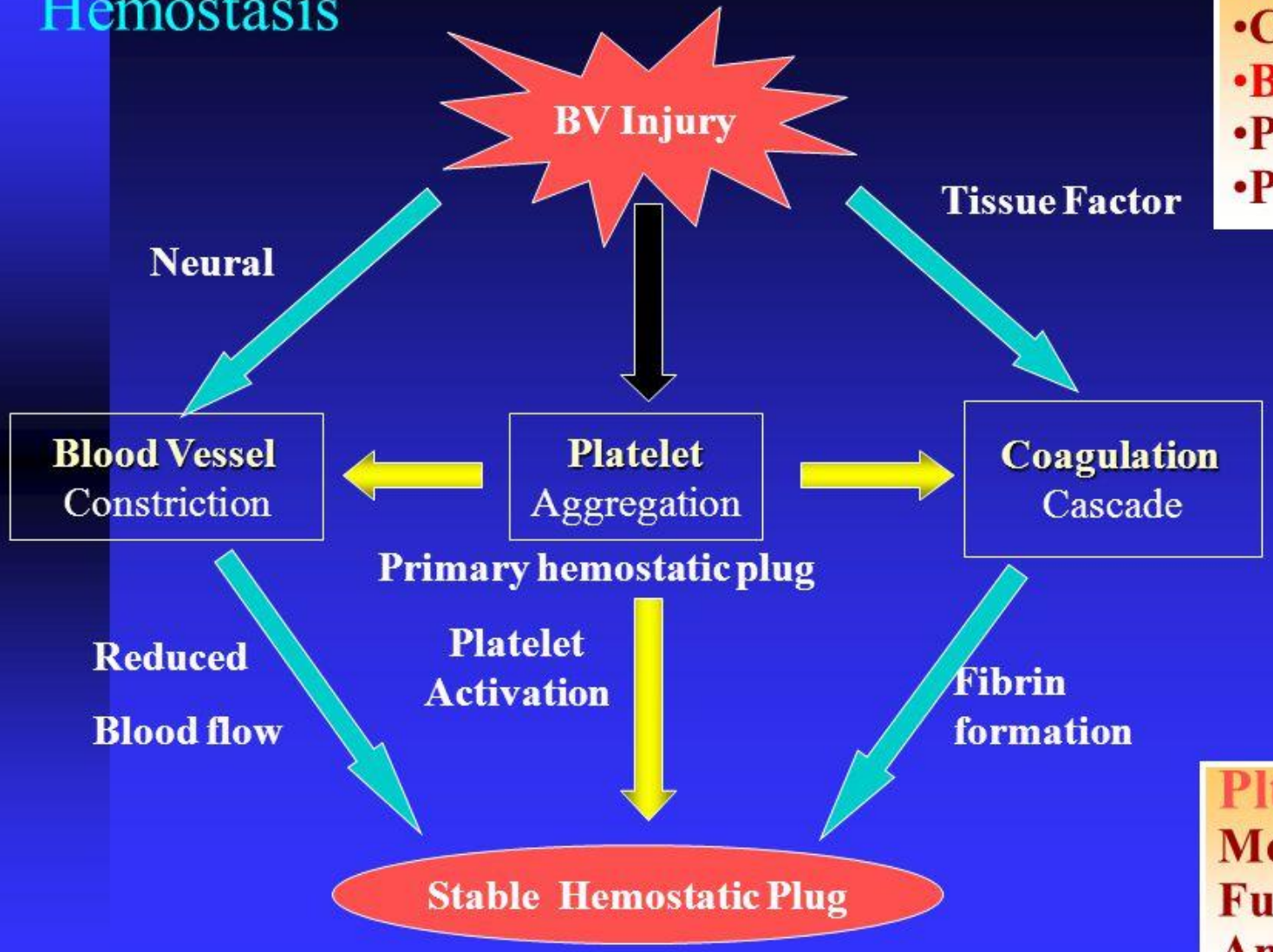
The cessation of bleeding following trauma to blood vessels results from three processes:

(i) the contraction of vessel walls;

(ii) the formation of a platelet plug at the site of the break in the vessel wall; and

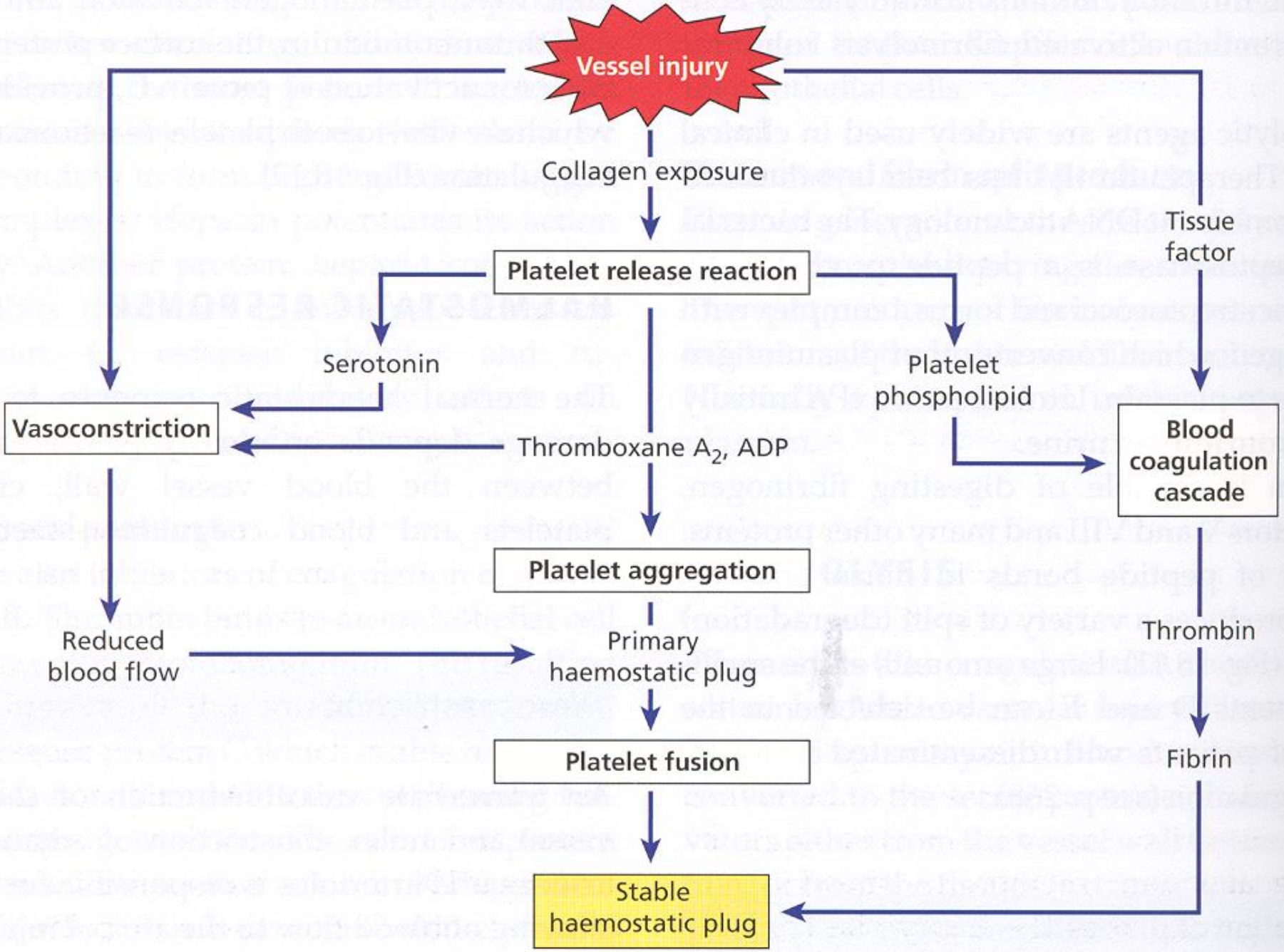
(iii) the formation of a fibrin clot.

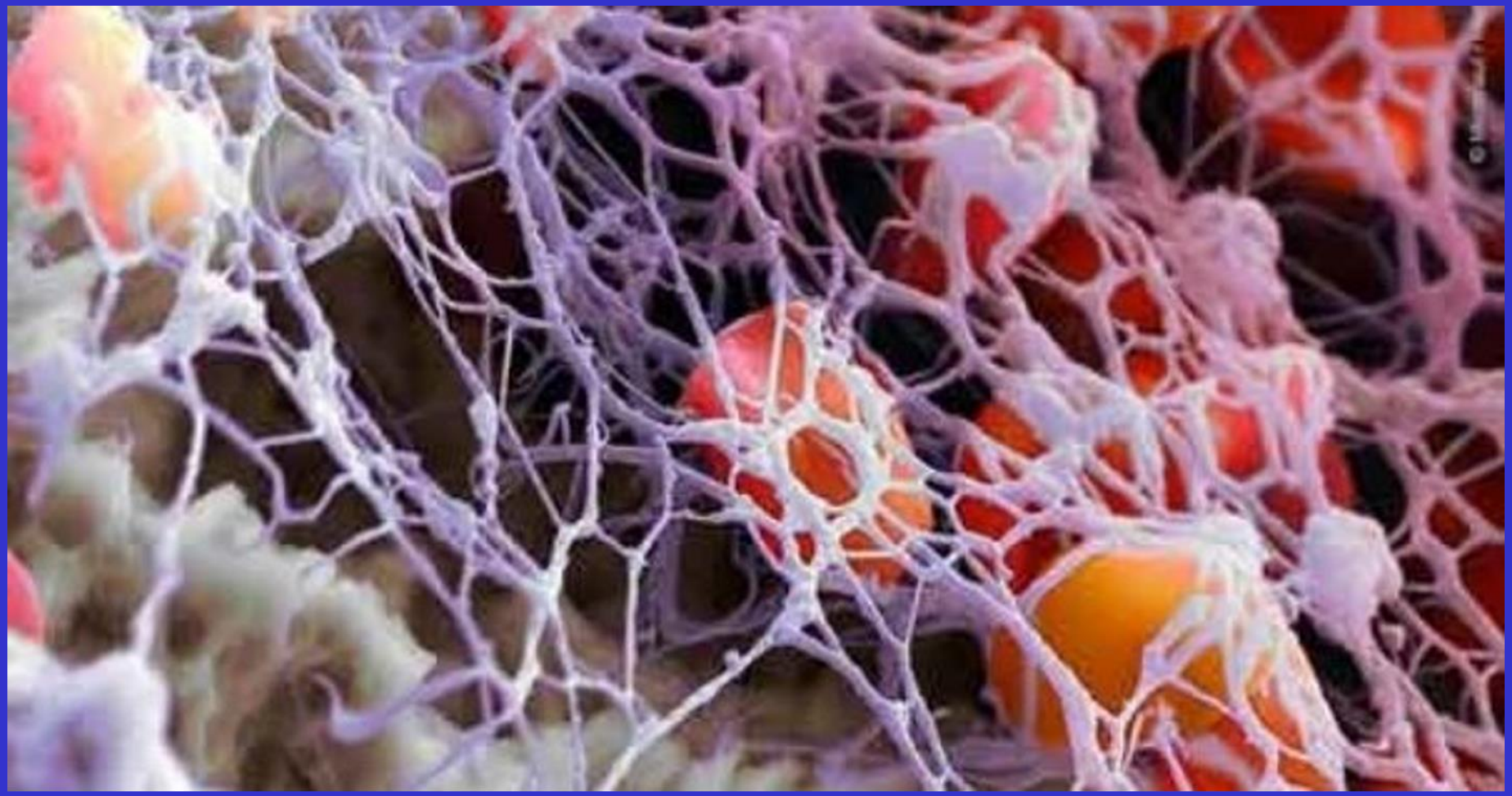
Hemostasis



Lab Tests
- CBC-Plt
- BT,(CT)
- PT
- PTT

Plt Study
- Morphology
- Function
- Antibody


Vessel injury
Collagen exposure
Platelet release reaction
Tissue factor
Serotonin
Platelet phospholipid
Vasoconstriction
Thromboxane A_2, ADP
Blood coagulation cascade
Platelet aggregation
Reduced blood flow
Primary haemostatic plug
Thrombin
Platelet fusion
Fibrin
Stable haemostatic plug

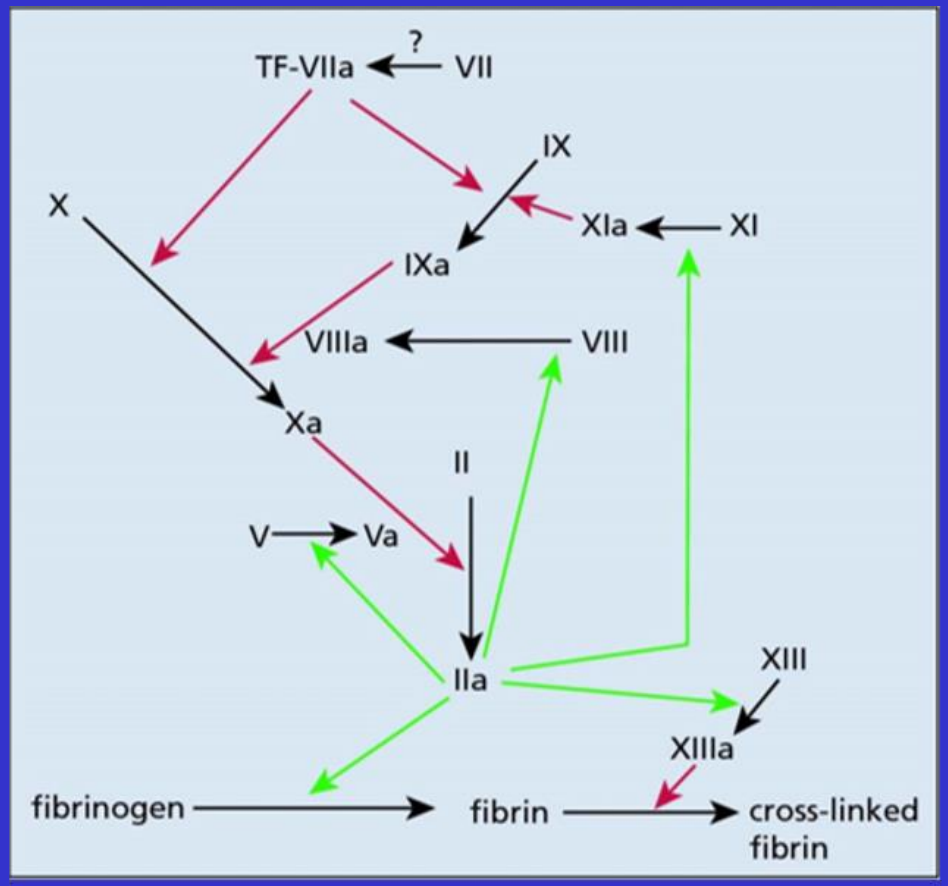


Early platelet fibrin hemostatic plug.

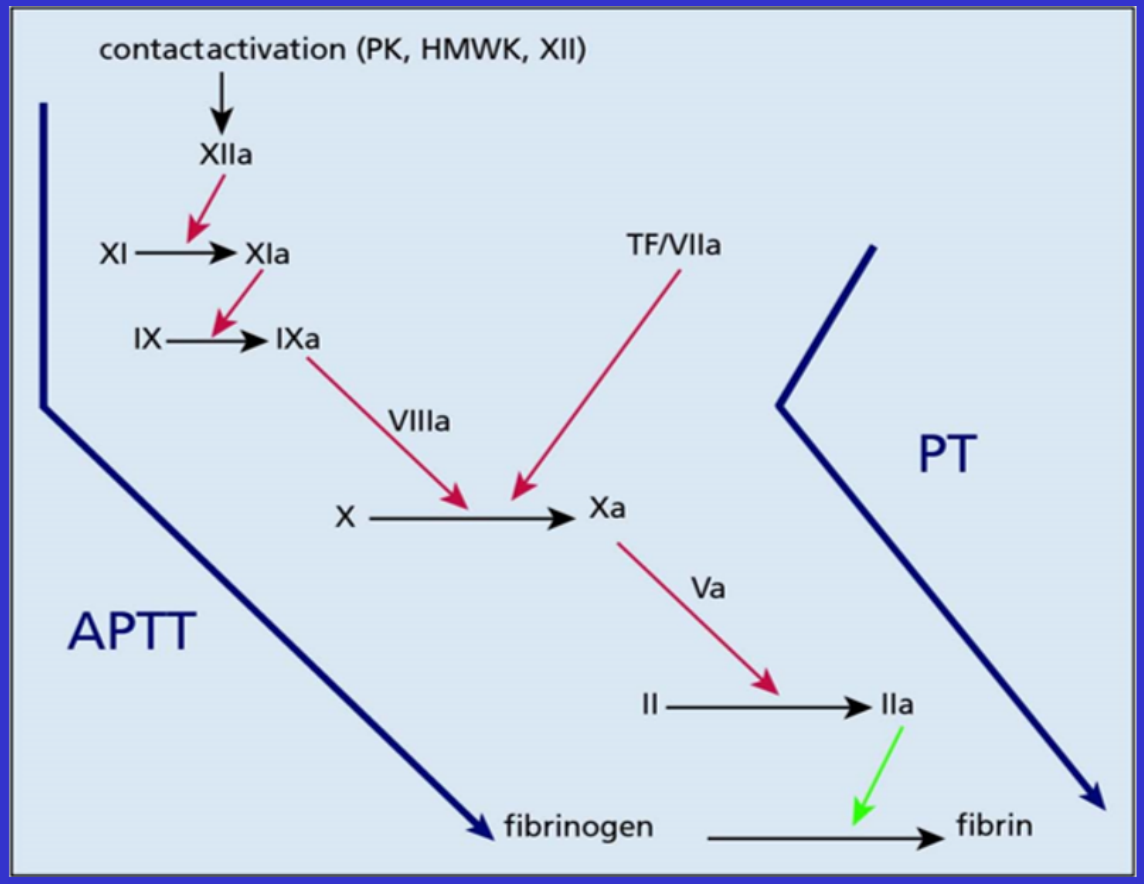
Late platelet fibrin hemostatic plug.

Normal coagulation mechanism

- The mechanisms involved in the clotting cascade were elucidated in the period 1950-70.
- The clotting sequence is initiated *in vivo* by tissue factor (TF) exposed on the surface of activated endothelial cells and leucocytes and on most extravascular cells in an area of tissue damage.
- Calcium is required at several stages in the coagulation sequence.



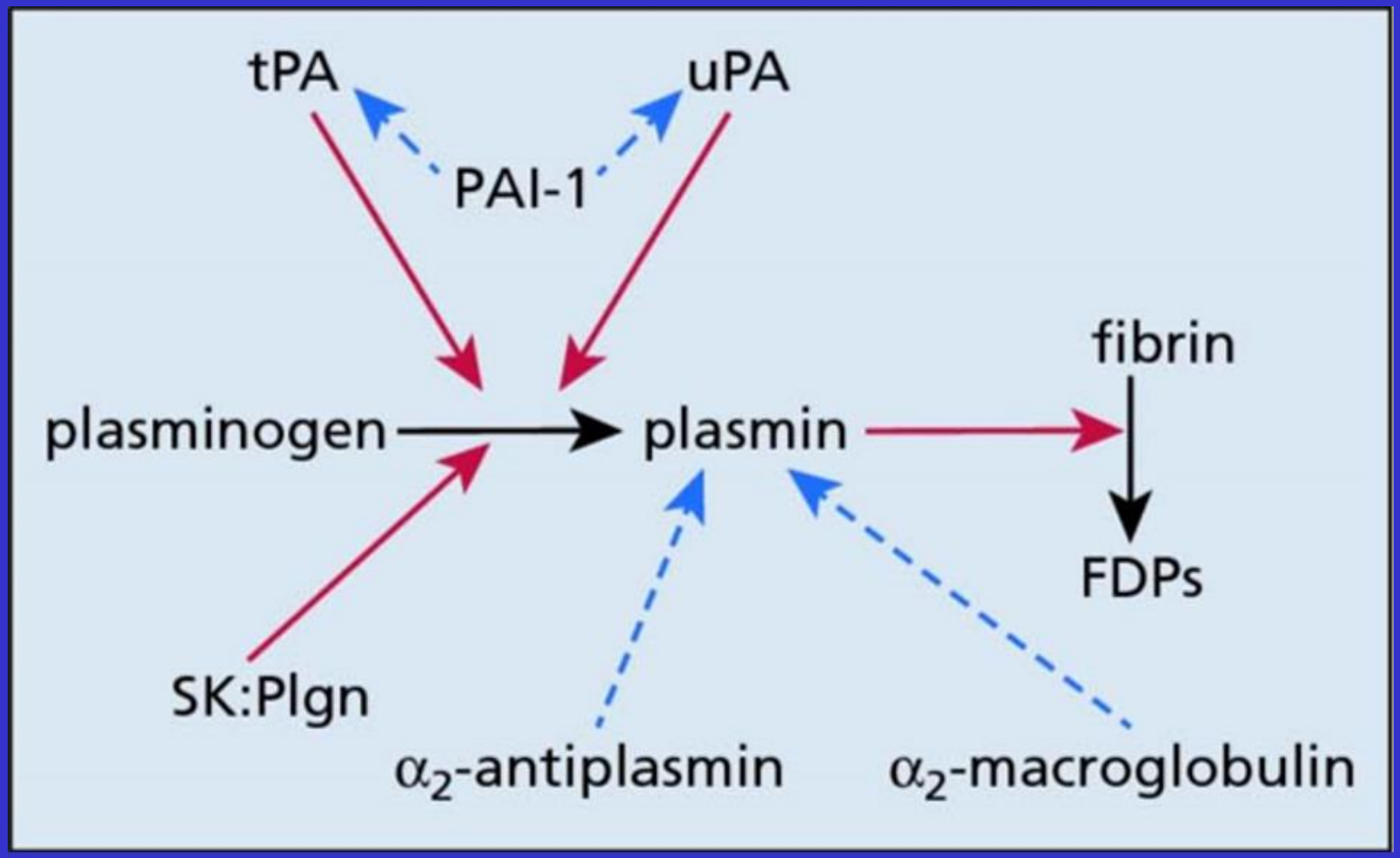
Pathways involved in fibrin generation after the activation of coagulation *in vivo* by TF. The suffix 'a' denotes the active form of each coagulation factor. *Notes:* Green arrows - actions of thrombin; red arrows - actions of other active enzymes; dashed blue arrows - inhibition.



The sequence of coagulation *in vitro* brought about by either contact activation of factor XII or by addition of tissue factor. The suffix 'a' denotes the active form of each coagulation factor. The former is the basis of the activated partial thromboplastin time (APTT) and the latter the prothrombin time (PT).

The fibrinolytic mechanism

After haemostasis has been achieved, the body has a mechanism for the enzymatic lysis of clots. The dissolution of the fibrin into fibrin-degradation products (FDPs) is carried out by the proteolytic plasma enzyme plasmin. Plasmin is present in the plasma in an inactive form.



The fibrinolytic mechanism.

Tests for clotting defects

There are three basic tests that are widely used, all performed on platelet-poor plasma obtained by centrifugation:

1) The *activated partial thromboplastin time* (APTT), which estimates the activity of factors XII, XI, IX, VIII, X, V, II and fibrinogen (the 'intrinsic system').
2) The *prothrombin time* (PT), which estimates the activity of factors VII, X, V, II and fibrinogen (the 'extrinsic system').

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3) The *thrombin time*, adding thrombin to plasma and measuring the time taken to clot, which is prolonged when there is an inherited or acquired deficiency of fibrinogen, or an inherited or acquired abnormal fibrinogen molecule (dysfibrinogenaemia) or in the presence of heparin or raised levels of FDPs.

Congenital coagulation disorders

- Blood clotting abnormalities can be conveniently divided into two categories, congenital defects and acquired defects.
- There is a group of patients who complain of excessive bleeding, either spontaneous or following trauma, usually starting early in life, and who frequently have a family history of a similar condition.
- These patients usually have one of three diseases:

1) haemophilia A (Factor VIII deficiency)
2) haemophilia B (Factor IX deficiency)
3) haemophilia C (Factor XI deficiency)
4) VWD

Haemophilia A (factor VIII deficiency)

- The term ‘haemophilia’, first used by Schönlein in 1839, was applied to a lifelong tendency to prolonged haemorrhage found in males and dependent on the transmission of a sex-linked abnormal gene.
- Patients with factor VIII deficiency and those with factor IX deficiency.

THE BLEEDING DISORDERS INCLUDE

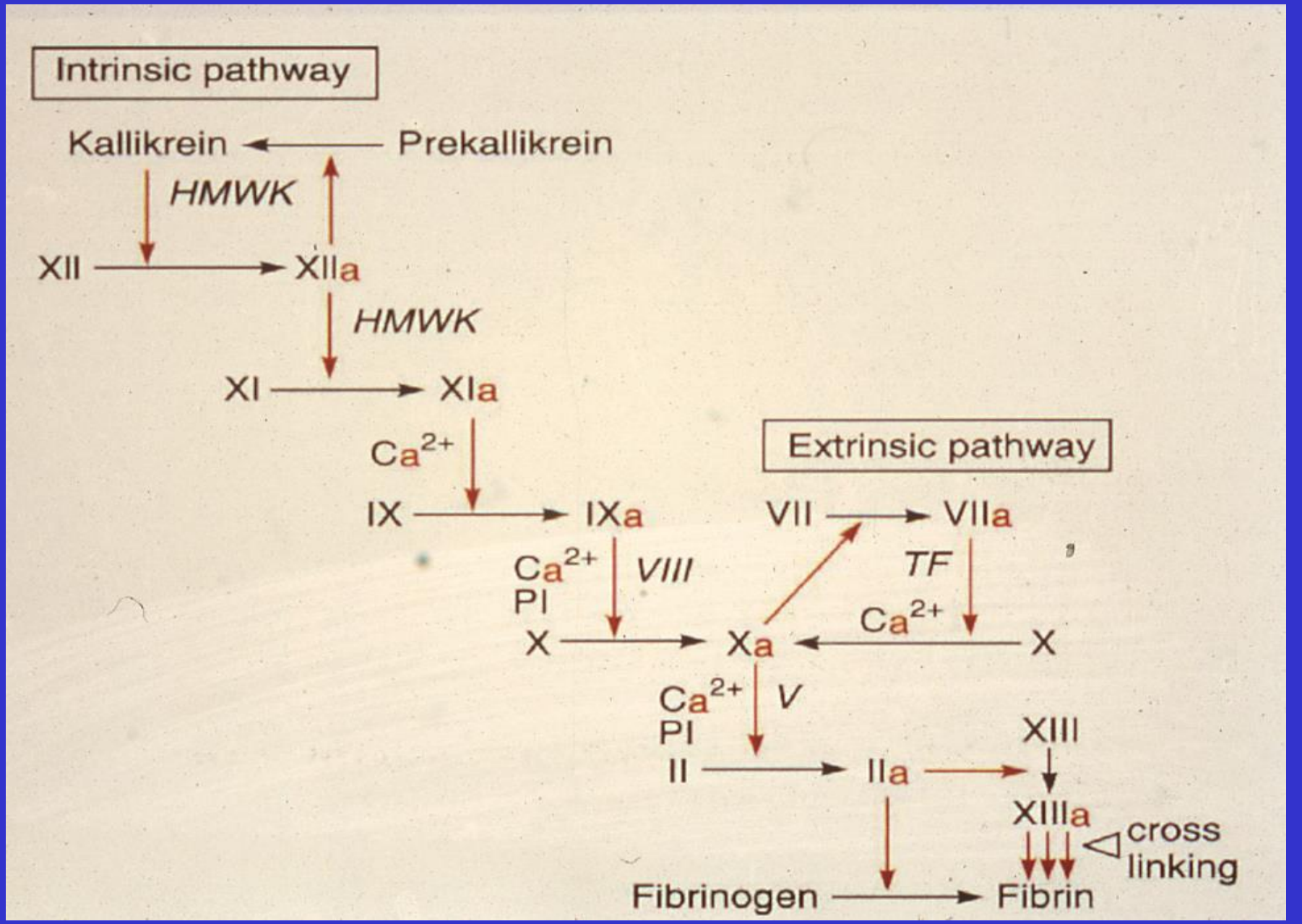
- Inherited and acquired blood vessel disorders
- Inherited and acquired platelets disorders
- Inherited and acquired coagulation disorders

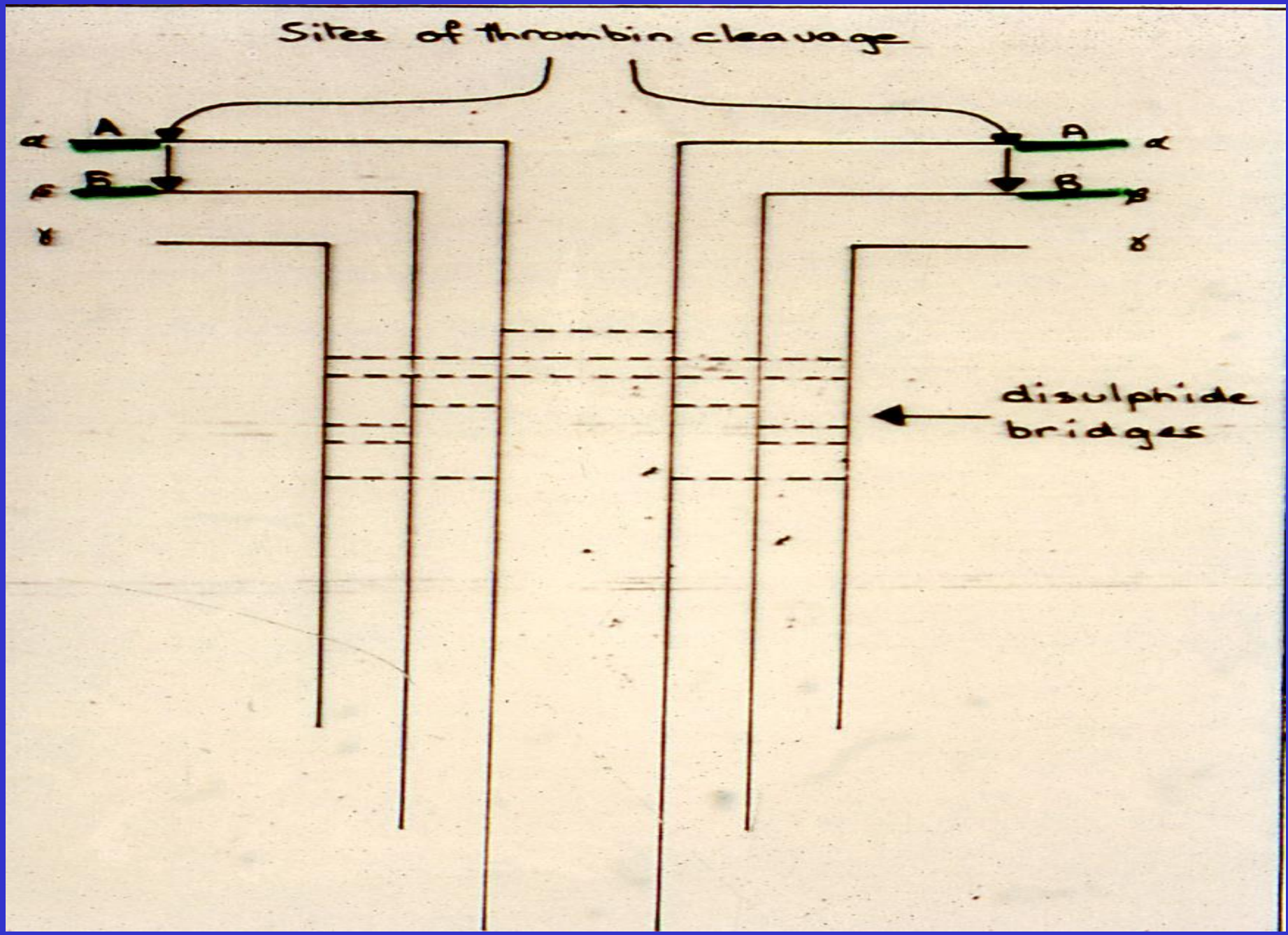
HEREDITARY COAGULATION DISORDERS

HAEMOSTASIS

PLASMA COAGULATION FACTORS

FI	FIBRINOGEN	FIX	CHRISTMAS FACTOR	ATIII	ANTI-THROMBIN III
FII	PROTHROMBIN	FX	STUART-POWER FACTOR	–	PREKALLIKREIN (FLETCHER) FACTOR
FIII	TISSUE FACTOR	FXI	PLASMA THROMBOBLASTIN ANTECEDENT	–	HMW KININOGEN FITZGERALD FACTOR
FIV	CALCIUM IONS	FXII	HAGEMAN (CONTACT) FACTOR	TM	THROMBOMODULIN
FV	PROACCELERIN	FXIII	FIBRIN STABILISING FACTOR	TFPI	TISSUE FACTOR PATHWAY INHIBITOR
FVII	PROCONVERTIN	PC	PROTEIN C		
FVIII	ANTIHAEMOPHILIC FACTOR	PS	PROTEIN S		


Intrinsic pathway
Kallikrein
Prekallikrein
HMWK
XII
XIIa
HMWK
XI
XIa
Ca2+
IX
IXa
Extrinsic pathway
VII
VIIa
Ca2+
PI
VIII
TF
Ca2+
X
Xa
X
Ca2+
PI
V
XIII
II
IIa
XIIIa
cross
linking
Fibrinogen
Fibrin


Sites of thrombin cleavage
A
B
α
β
γ
A
B
α
β
γ
disulphide bridges

Thrombin

Fibrinogen → Fibrin monomer + peptides A & B

Fibrin Manomers ⇄ Aggregates

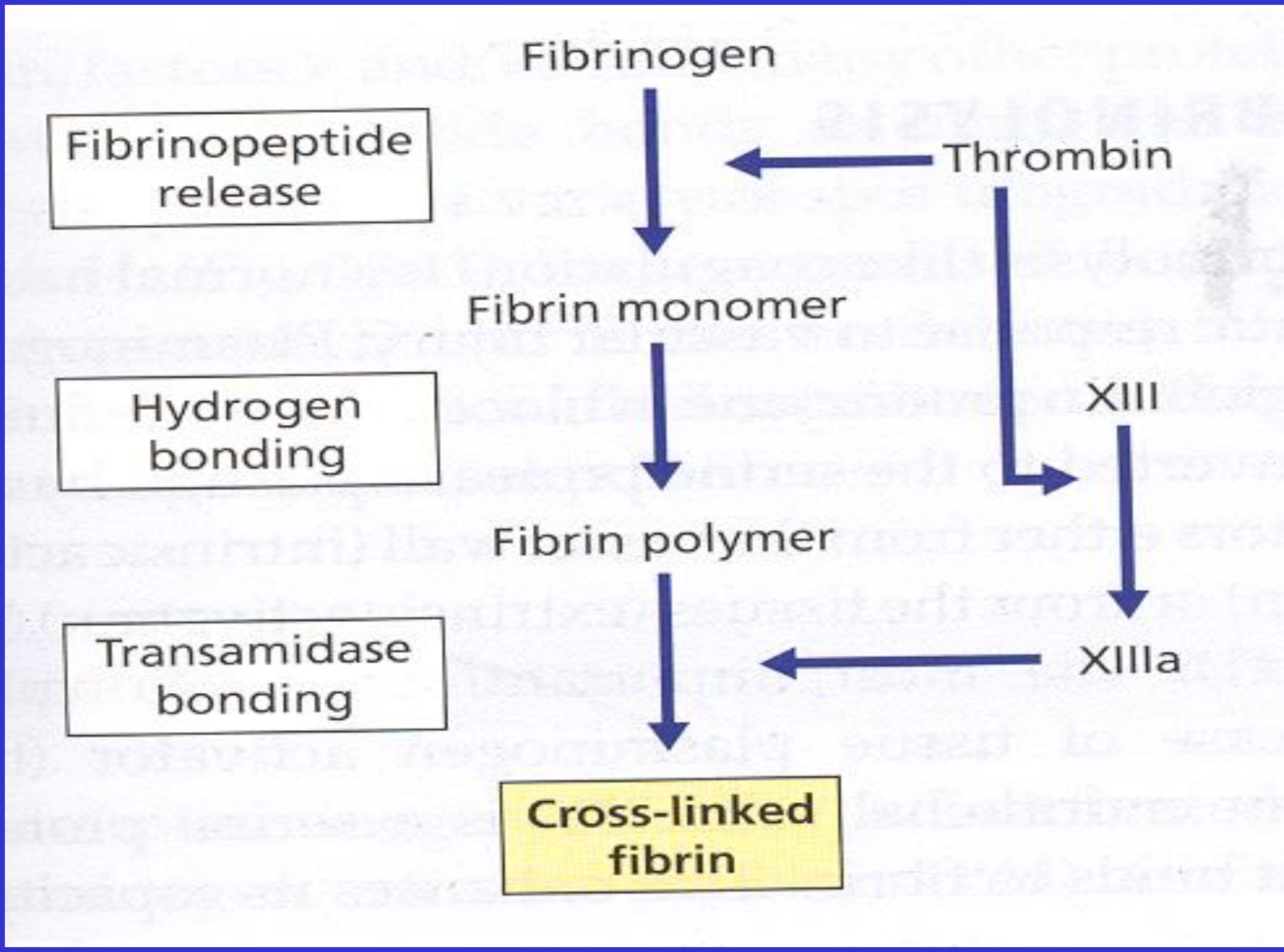
Fibrin Aggregates ⇄ Fibrin $_s$ (polymerisation)

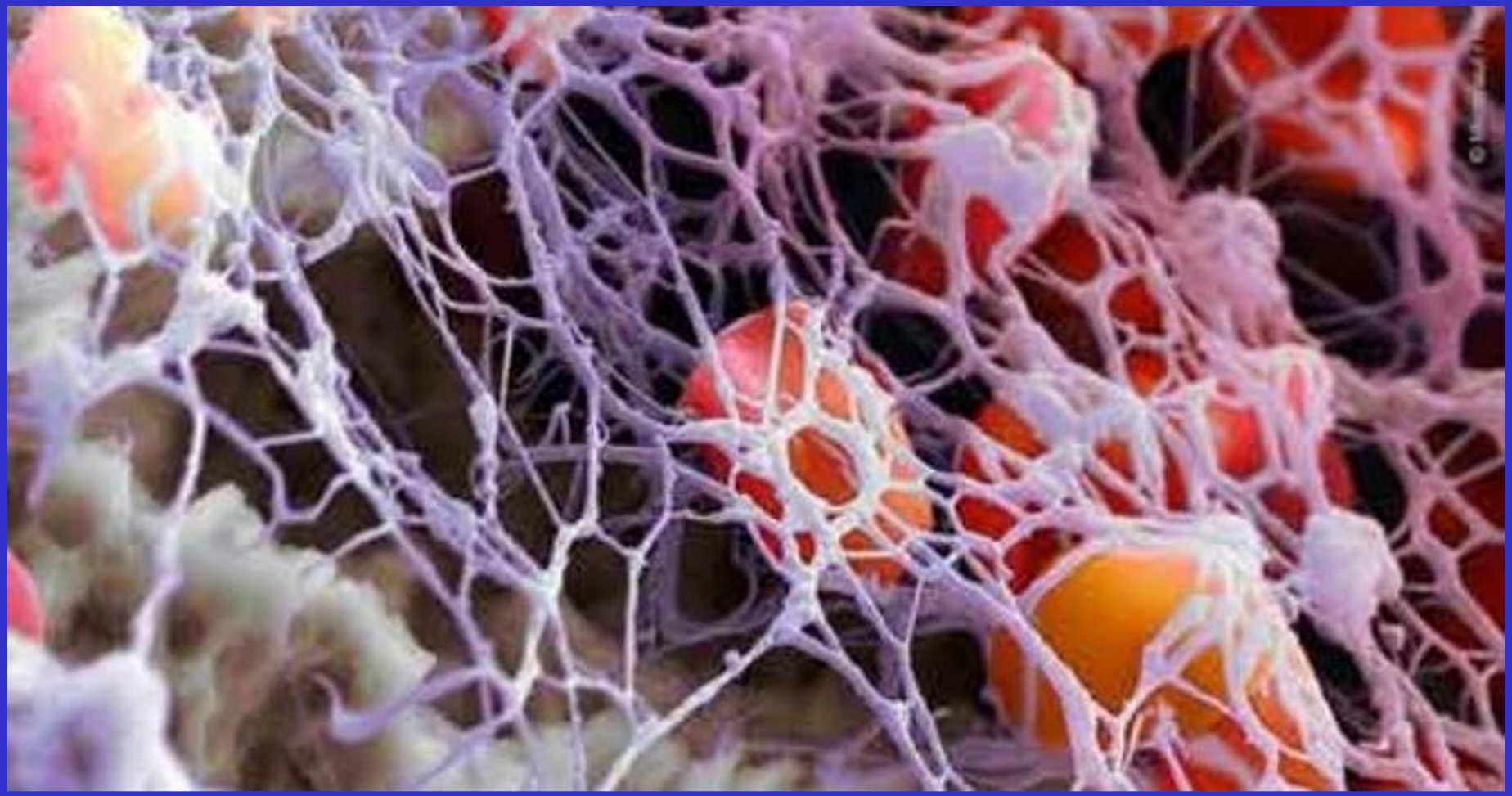
Fibrin $_s$ ⟶ Fibrin $_i$ (cross linked)

↑ XIII

Fibrin $_s$ = Soluble in 5m urea

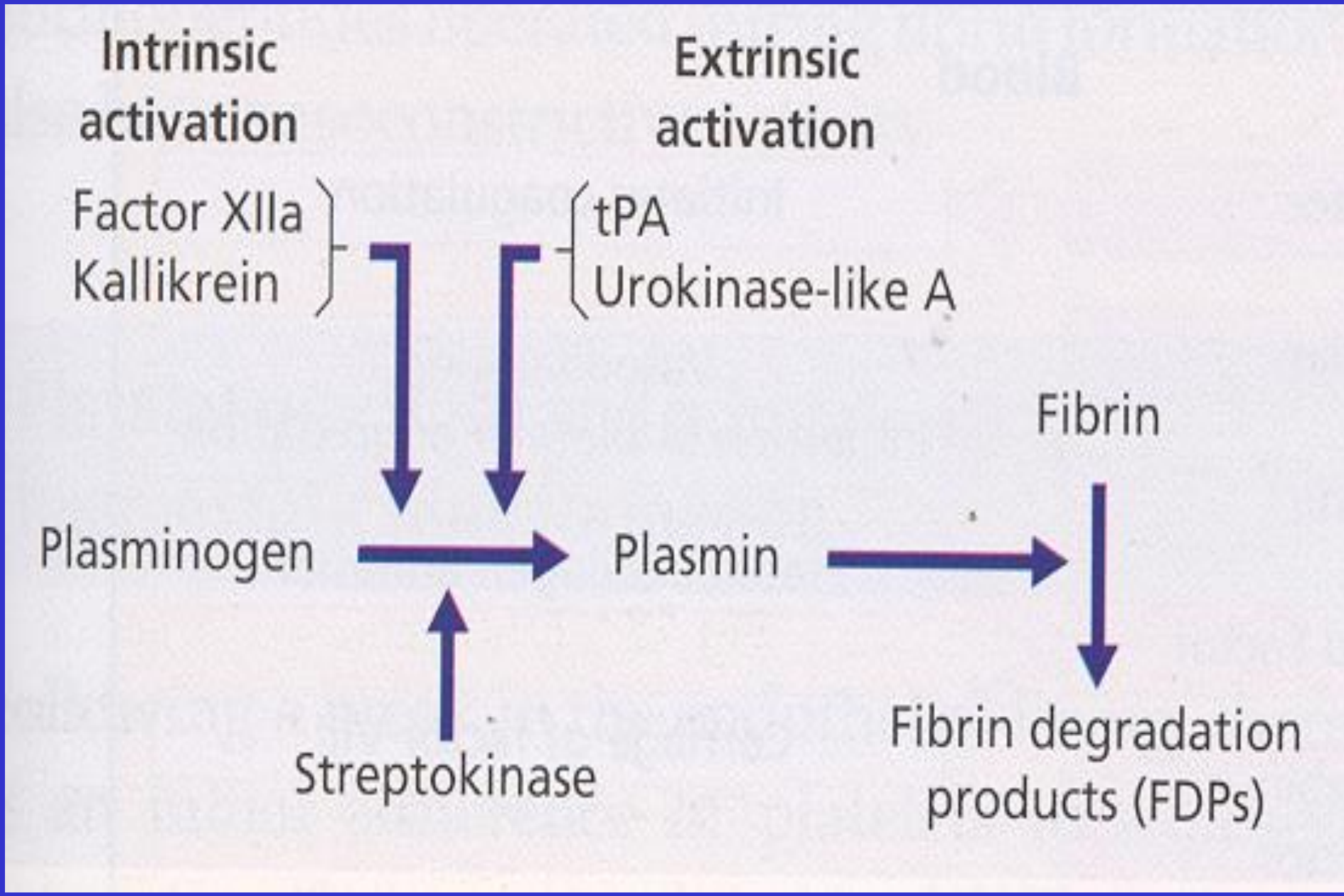
Fibrin $_i$ = Insoluble in 5m urea


Fibrinogen
Fibrinopeptide release
Thrombin
Fibrin monomer
Hydrogen bonding
XIII
Fibrin polymer
Transamidase bonding
XIIIa
Cross-linked fibrin



Early platelet fibrin hemostatic plug.

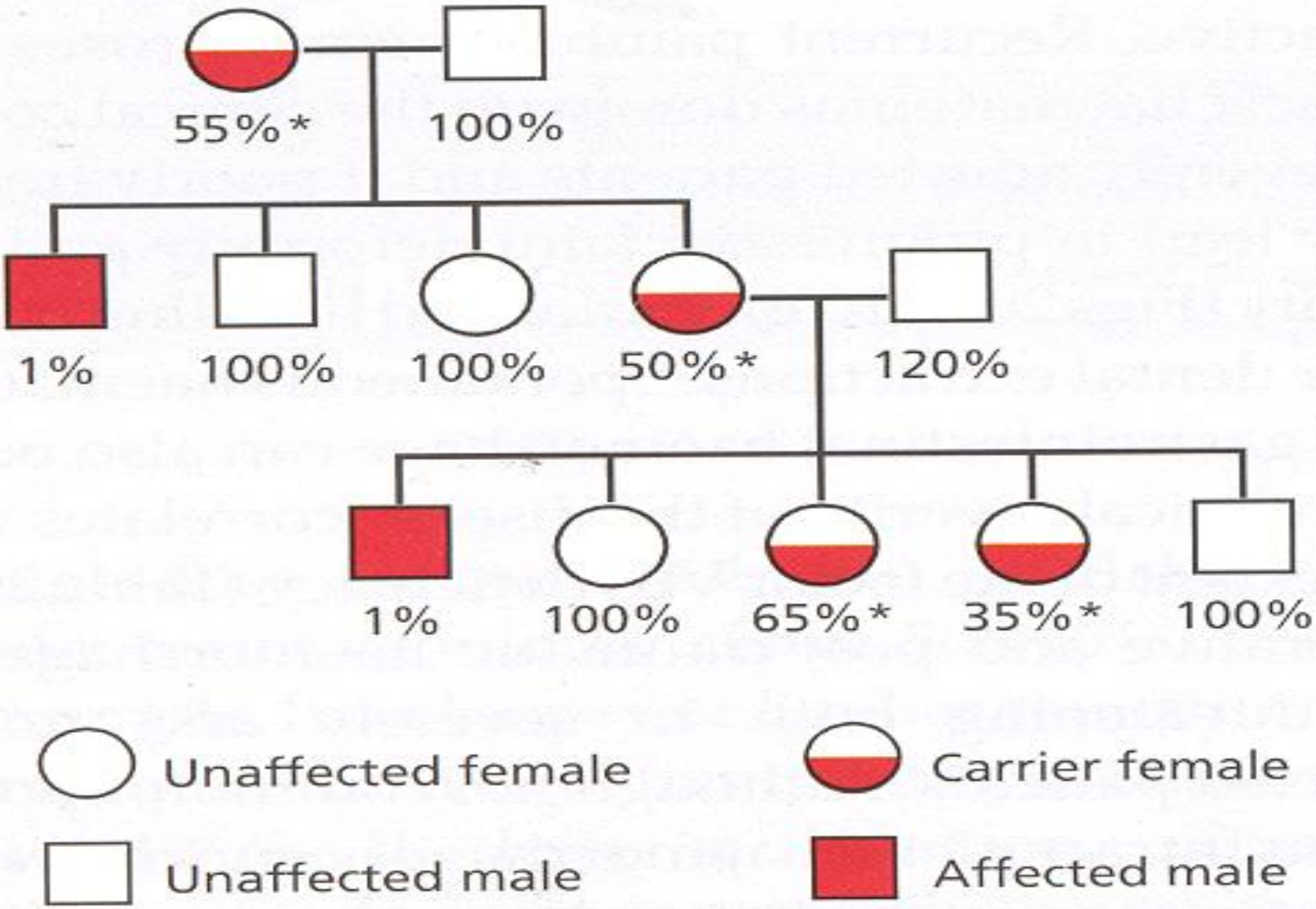
Late platelet fibrin hemostatic plug.


Intrinsic activation
Extrinsic activation
Factor XIIa
Kallikrein
tPA
Urokinase-like A
Fibrin
Plasminogen
Plasmin
Streptokinase
Fibrin degradation products (FDPs)

INHERITED COAGULATION DISORDERS

HAEMOPHILIA

- Factor VIII Deficiency
- Factor IX Deficiency (Christmas Disease)
- Factor XI Deficiency
- Von Willebrand Disease
- Other Factors Deficiency


55%*
100%
1%
100%
100%
50%*
120%
1%
100%
65%*
35%*
100%
Unaffected female
Carrier female
Unaffected male
Affected male

CLINICAL FEATURES OF HAEMOPHILIA

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

Coagulation factor activity (percentage of normal)	Clinical manifestations
<1	Severe disease Frequent spontaneous bleeding episodes from early life Joint deformity and crippling if not adequately teated
1 - 5	Moderate disease Post-traumatic bleeding occasional spontaneous episodes
5 - 20	Mild diesease Post-traumatic bleeding

Detection of carriers and antenatal diagnosis

- Genetic mutational analysis allows carriers to be identified with accuracy and is the method of choice.
- Prenatal diagnosis of haemophilia can be made by analysis of fetal DNA, which can be obtained either by chorionic villus sampling between 11½ and 14 weeks of gestation or by amniocentesis after 16 weeks.

Clinical features

- The characteristic clinical feature of severe haemophilia is the occurrence of spontaneous bleeding into the joints and less frequently into the muscles.
- The presenting symptom is pain in the affected area and this can be very severe.
- Bleeding into joints results in crippling deformity.

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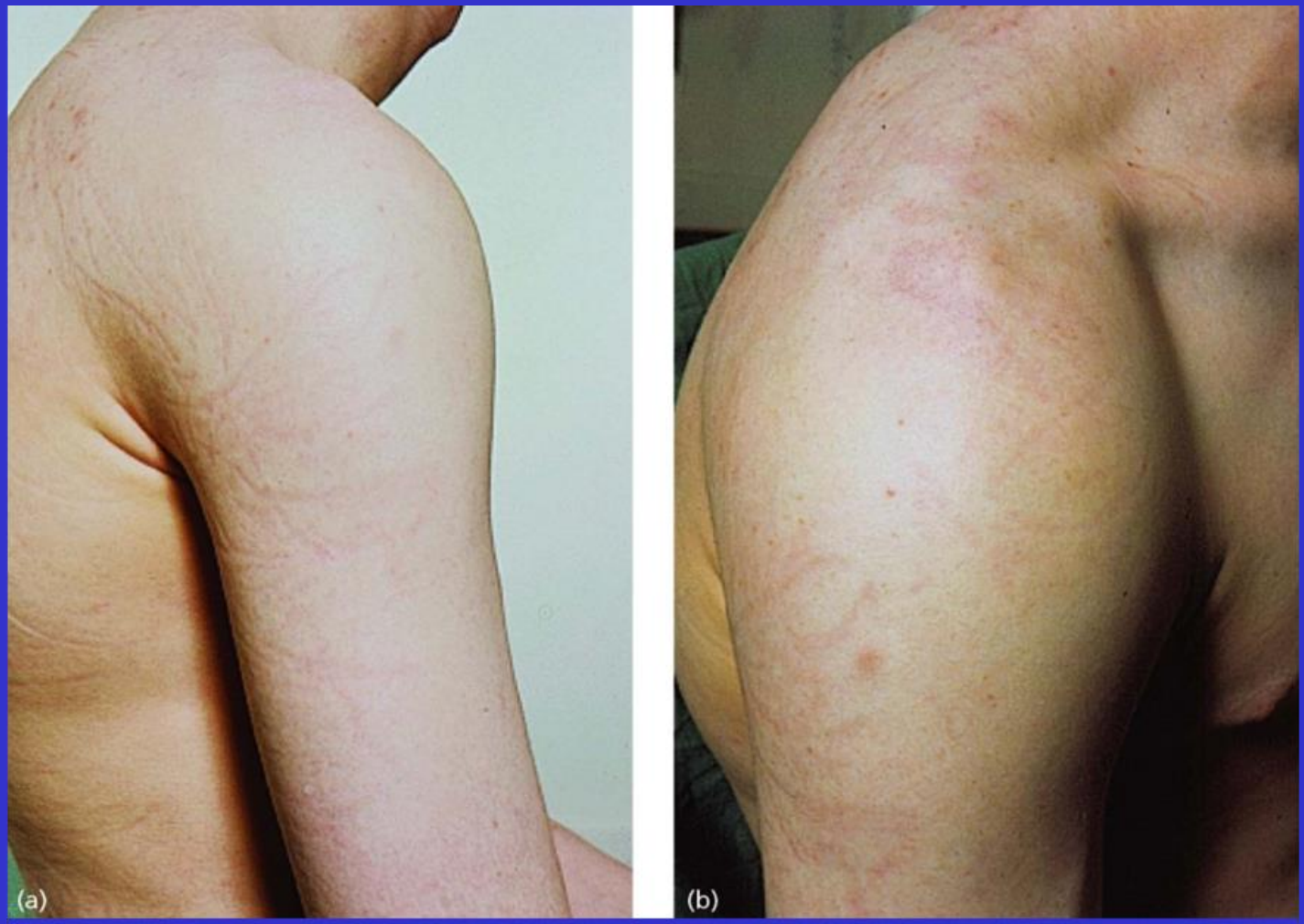
- The knees, elbows and ankles are most commonly affected.
- Haematuria, epistaxis and gastrointestinal bleeding are less common.
- Intracranial bleeding is the most common cause of death from the disease itself.



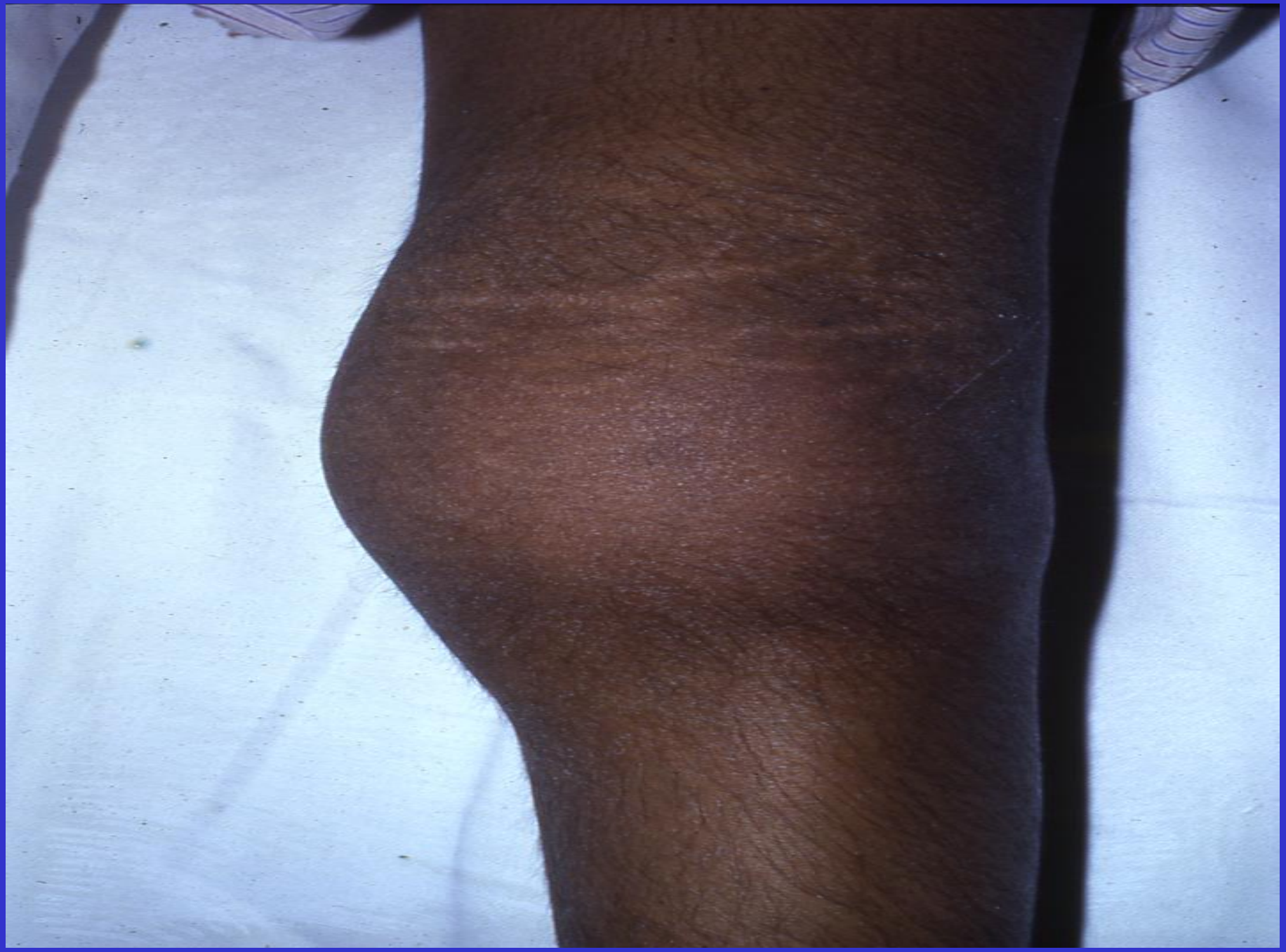
Haemarthrosis of the shoulder joint in a patient with haemophilia A.

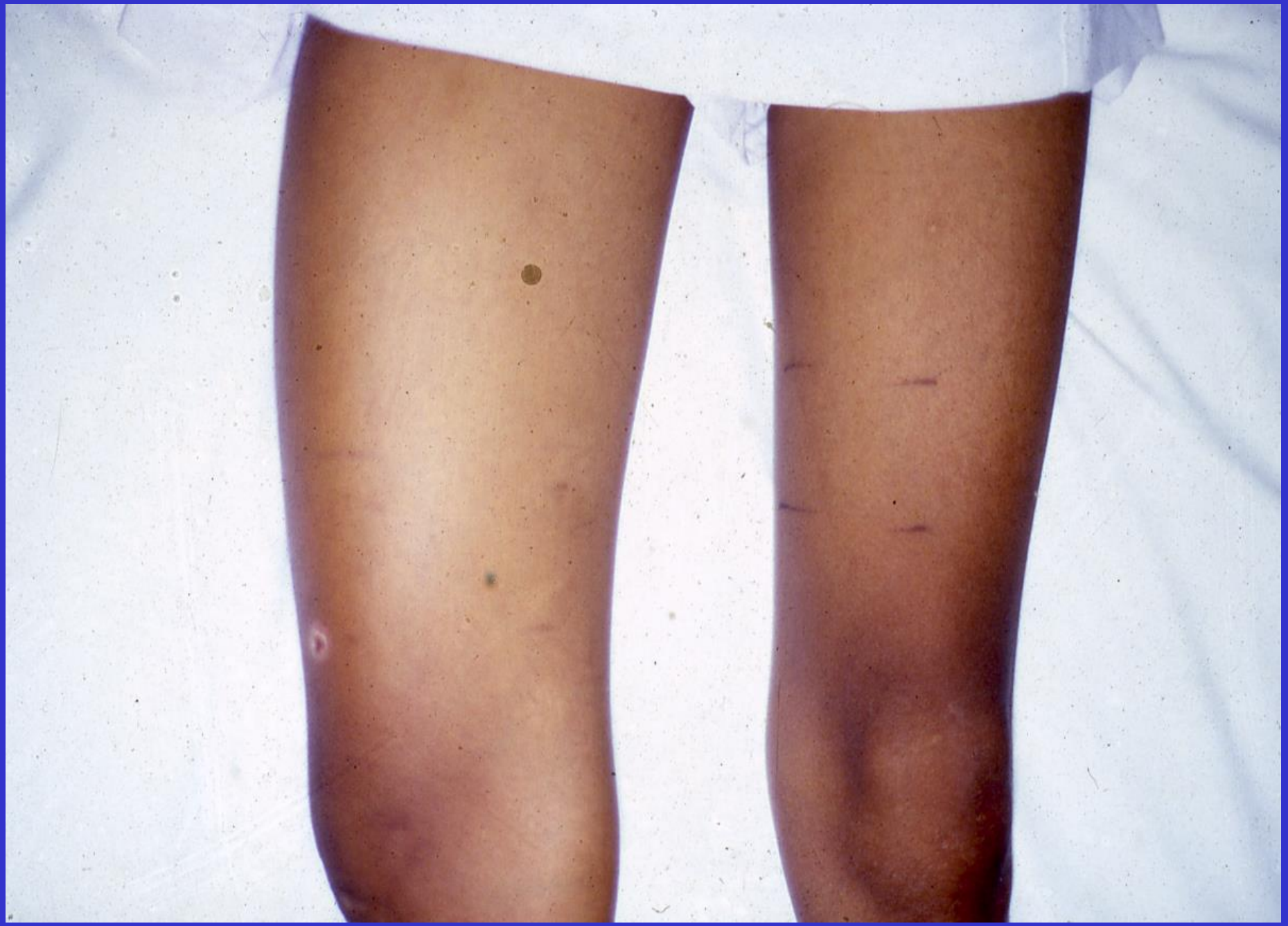
The frequency of bleeding sites in 207 haemophiliacs.

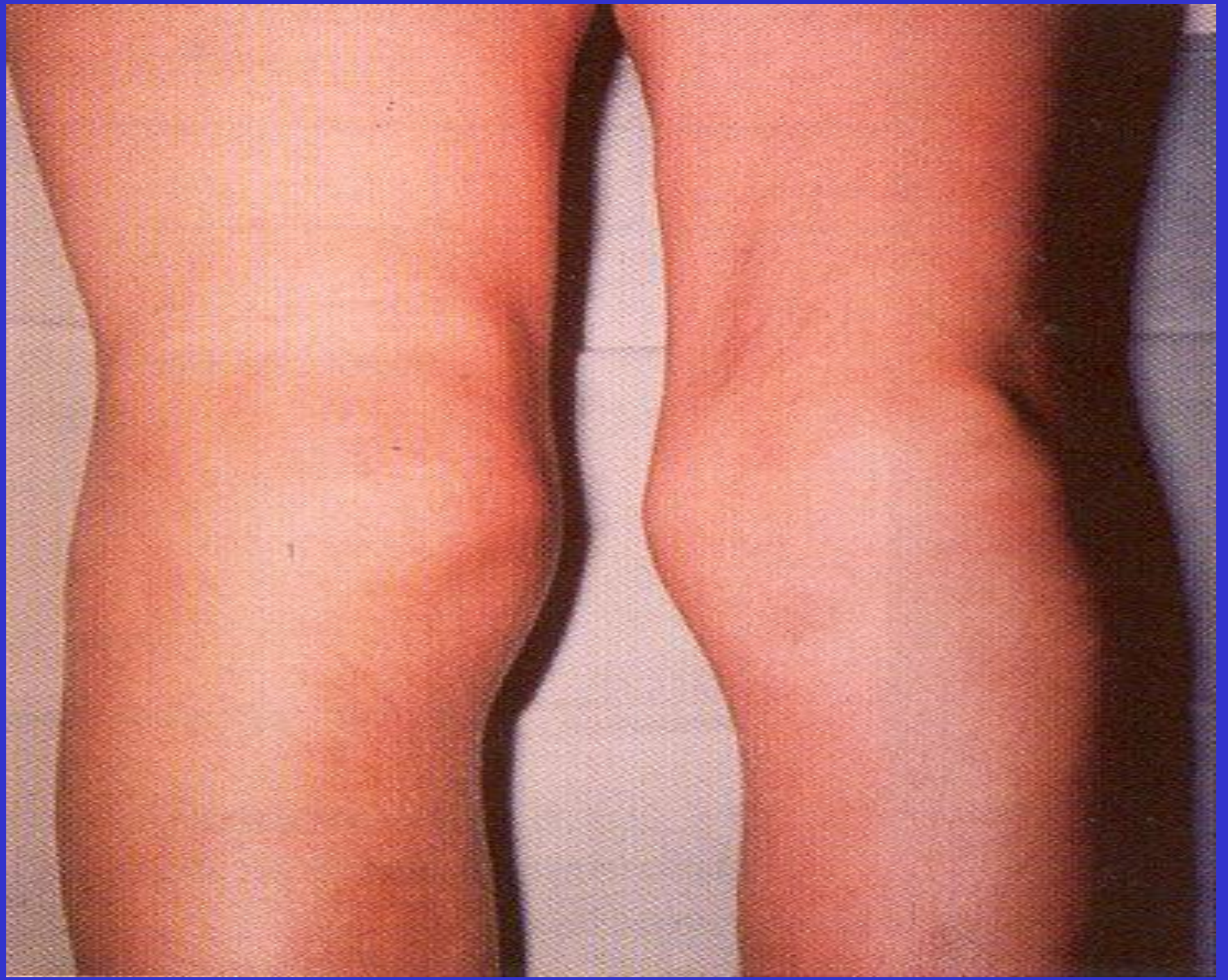
Lesion or operation	Percentage
Haemarthroses	79
Muscle haematomas	15
Haematuria	Each about 1-2 Total 6
Epistaxis	
Gastrointestinal bleeding	
Dental Extraction	
Major surgery	

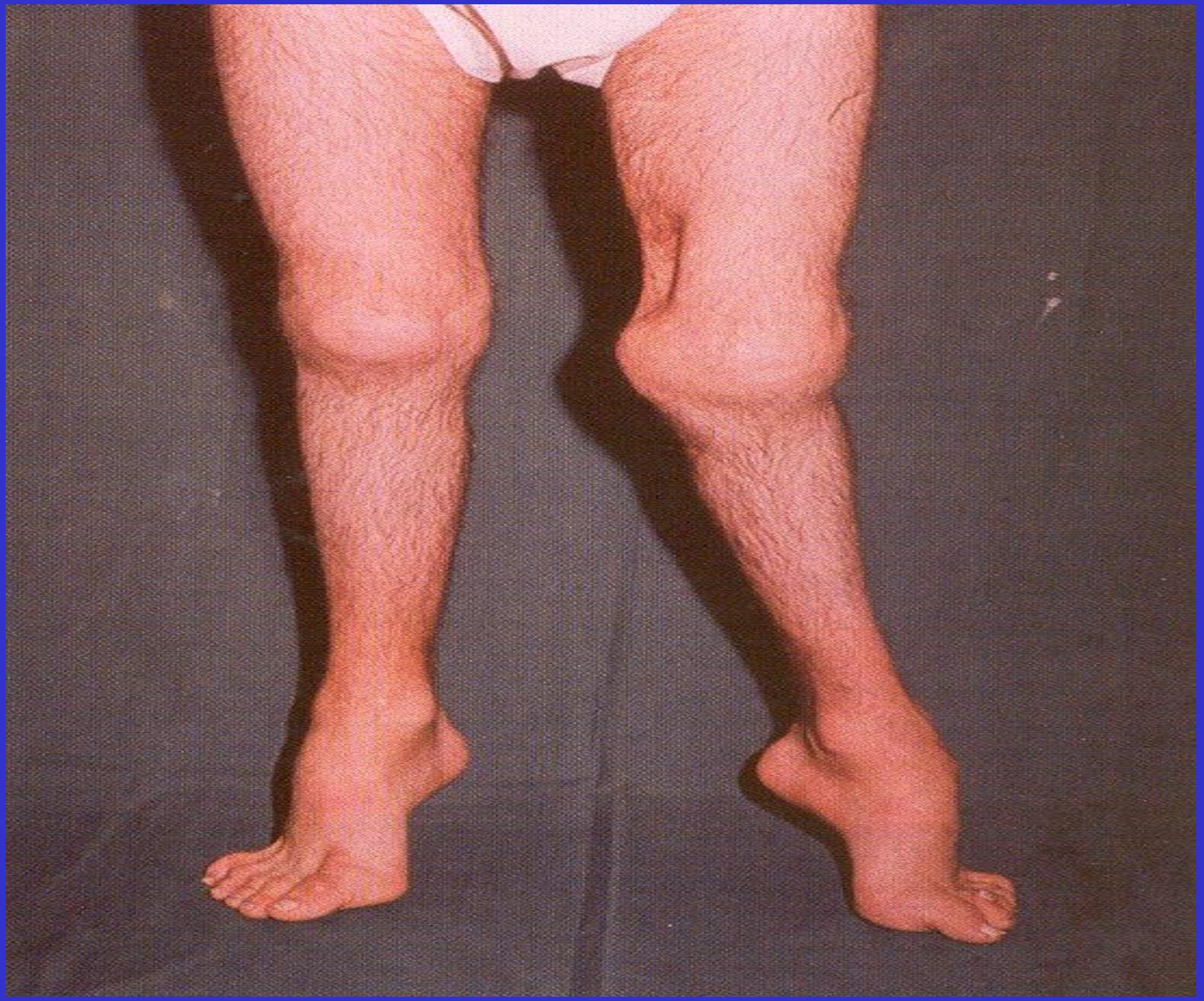
Diagnosis

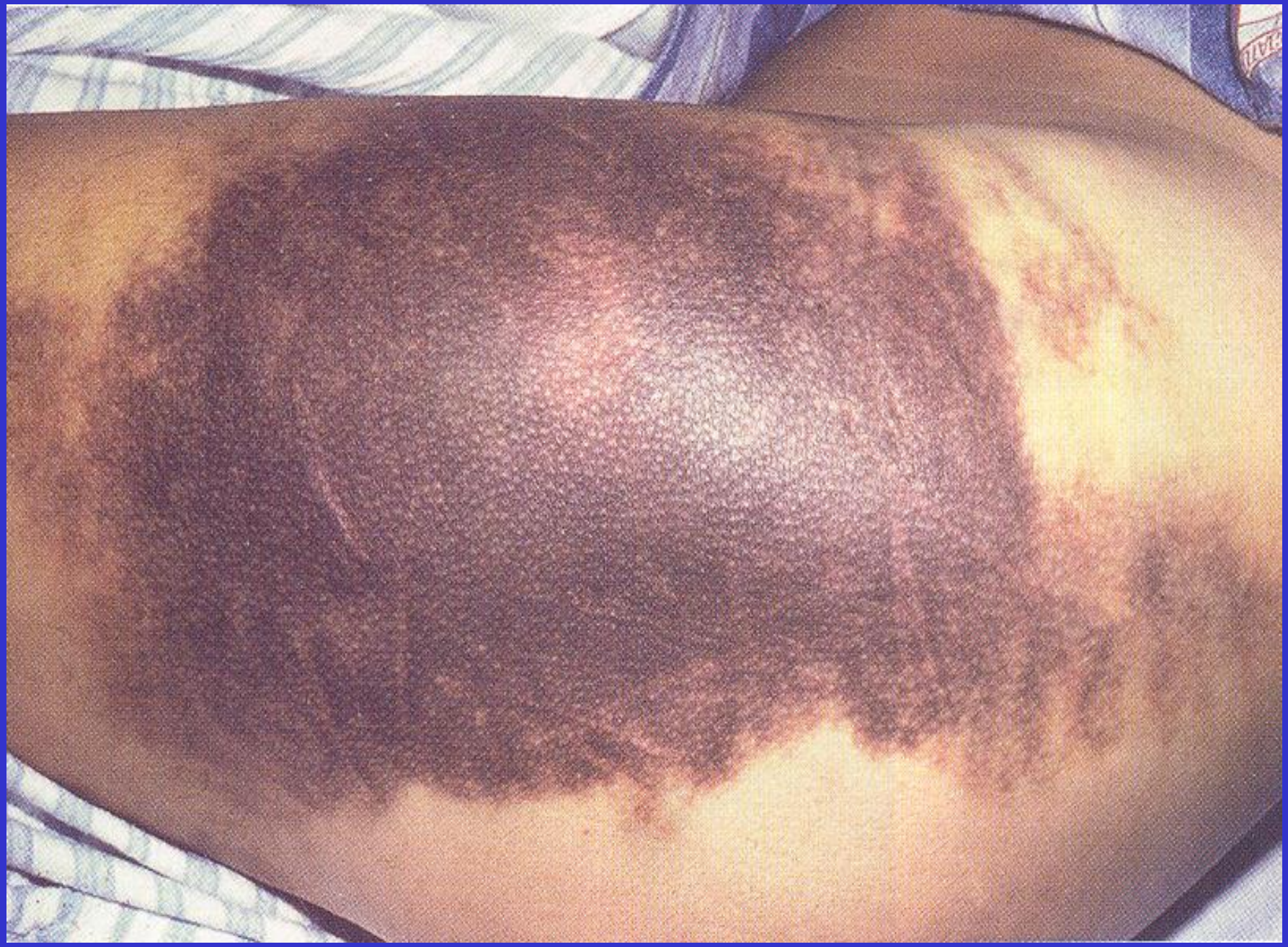
The possibility of haemophilia is suggested by the finding of a normal PT and a prolonged APTT. Confirmation is by a specific assay of factor VIII coagulant activity with normal VWF. The combination of a normal PT and a prolonged APTT is most often caused by lupus anticoagulant.

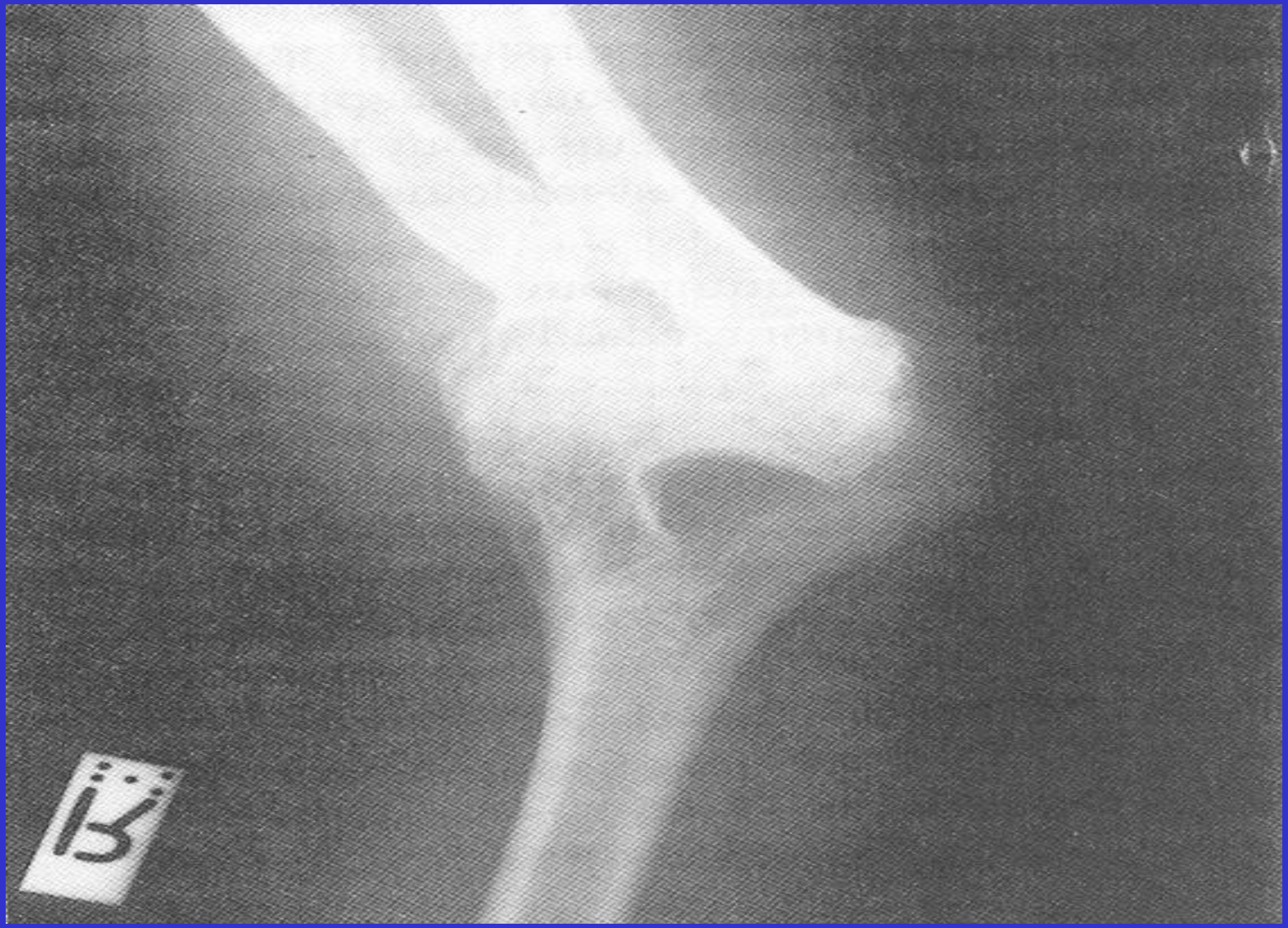


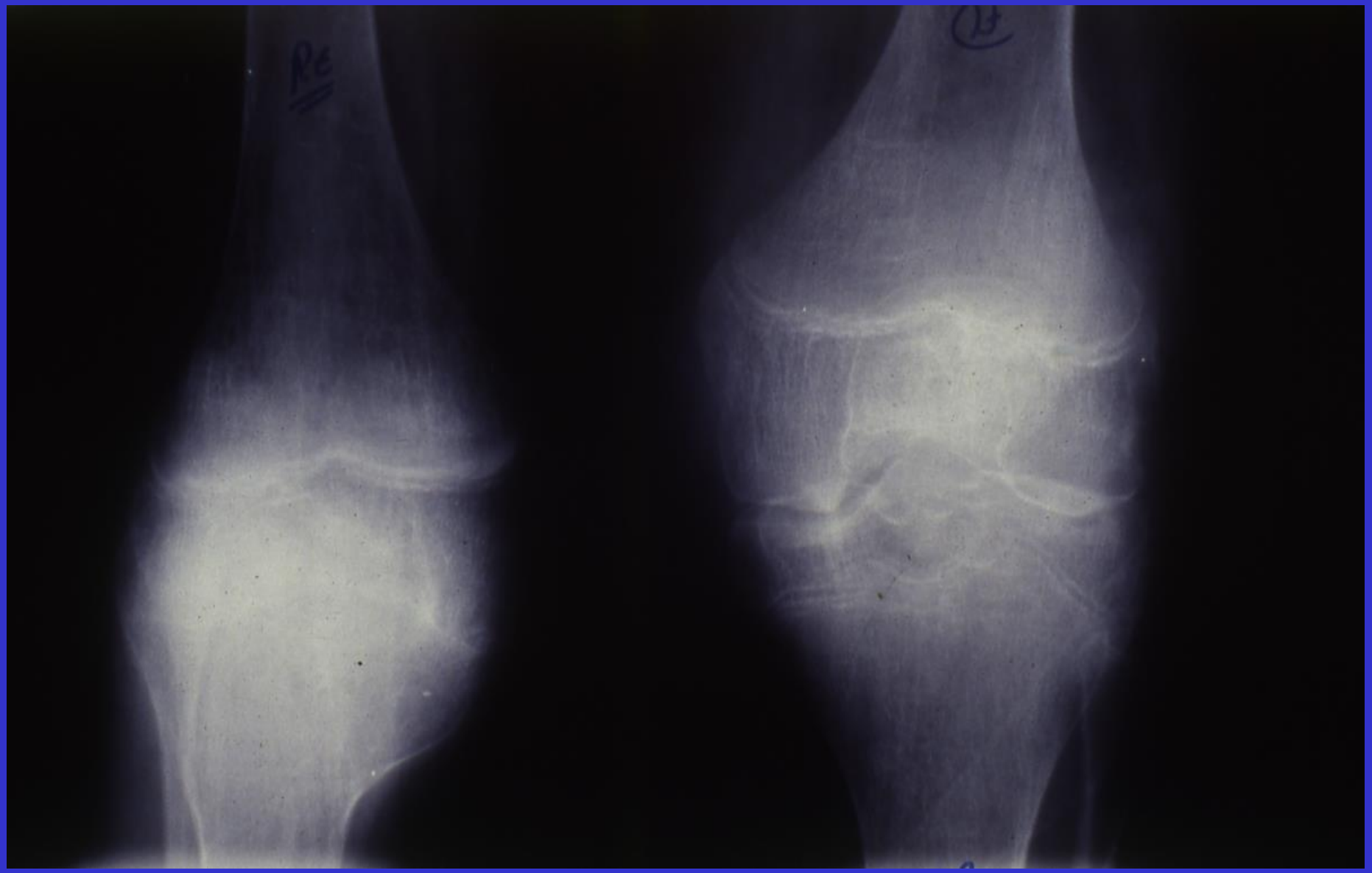


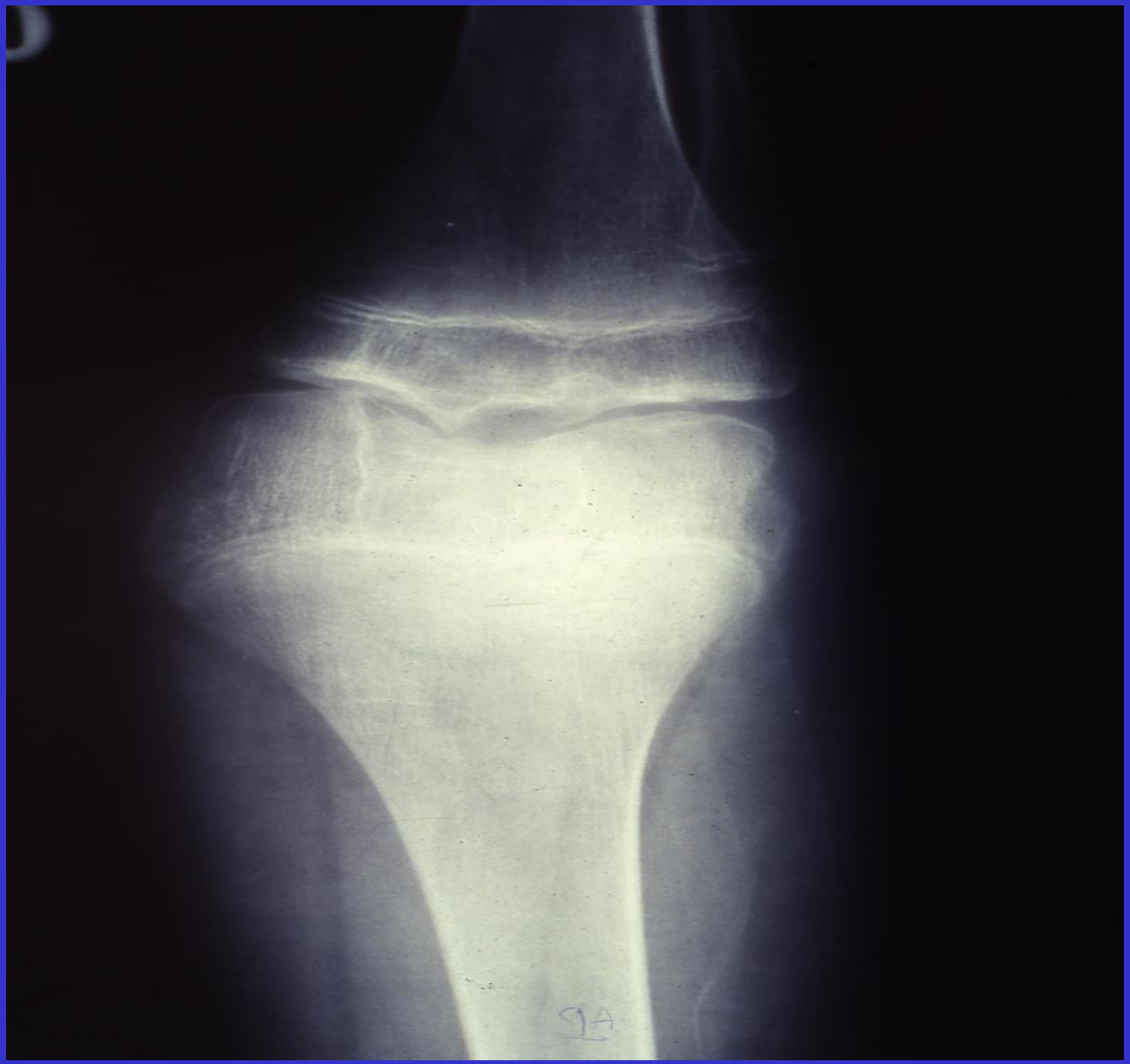


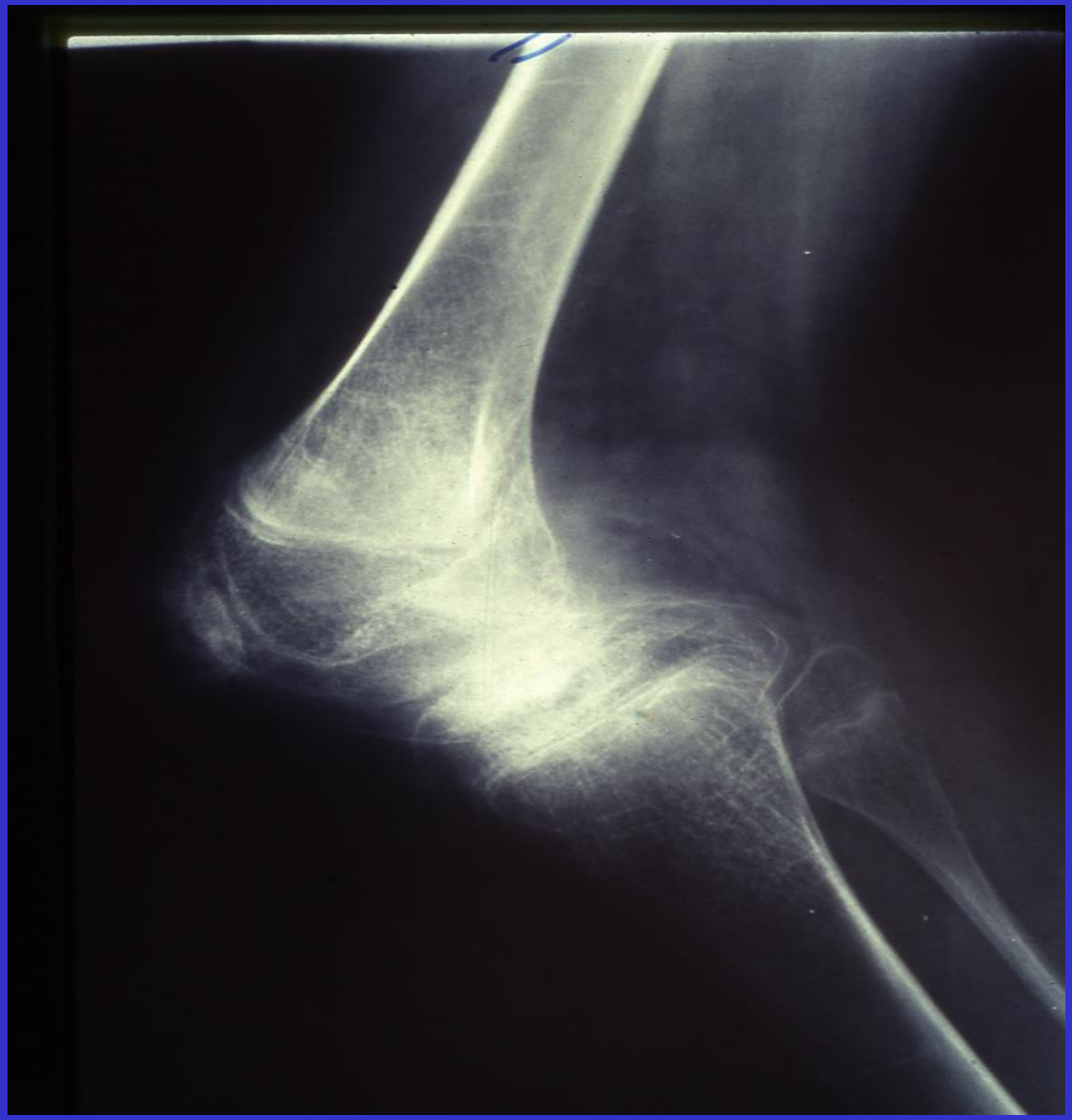












Treatment of Haemophilia

- Treatment should be given at the earliest sign of spontaneous or post-traumatic bleeding.
- Treatment consists of intravenous injections of virucidally treated plasma-derived high purity factor VIII concentrate or recombinant factor VIII preparations to maintain plasma factor VIII coagulant activity to between 30% and 100% of normal.
- Approximately 25% of patients with haemophilia, usually after treatment with factor VIII on 10-20 occasions, develop antibodies that inhibit its functional activity and in 5-10% of patients these are of high titre.

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- Haemorrhage in patients with high-titre inhibitors may require treatment with 'bypassing agents' such as recombinant factor VIIa or FEIBA (factor eight inhibitor bypassing activity; that is, a plasma-derived activated prothrombin complex concentrate), which activate the coagulation cascade below the level of factor VIII.
- The administration of factor VIII may be avoided in mild to moderate haemophilia by using the vasopressin analogue desmopressin (DDAVP), which causes a temporary increase in factor VIII and VWF by provoking the release of these factors from endothelial cells. DDAVP is used intravenously, subcutaneously or intranasally.

Deficiency of other clotting factors

Single deficiencies of factors other than VIII and IX are very rare, but all possible deficiencies have been found and all except contact factor (e.g. factor XII) deficiency give rise to bleeding disorders of varying degrees of severity.

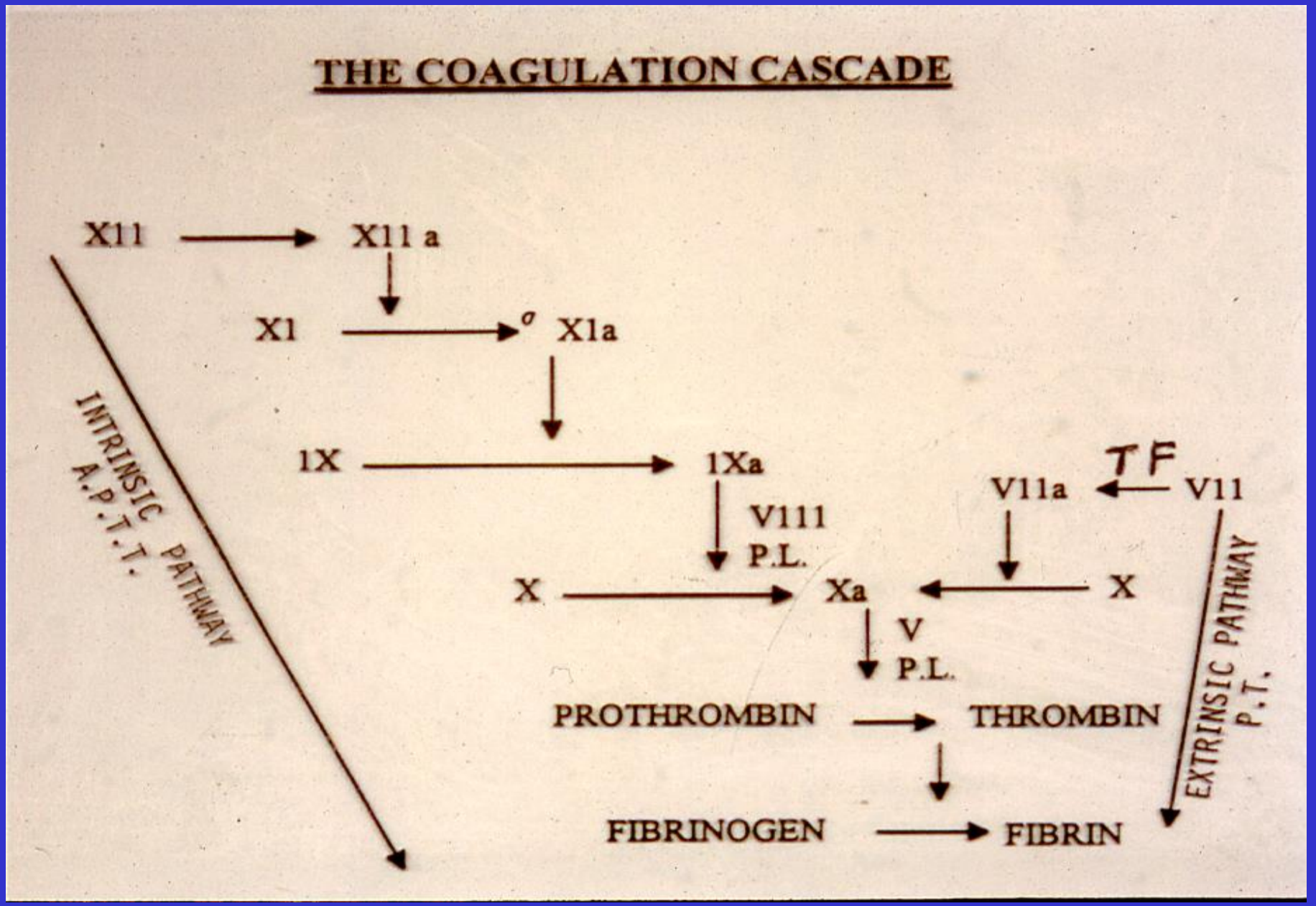
Acquired coagulation disorders

The hepatocytes are the major cell type involved in the synthesis of all the coagulation factors. Hence, severe liver disease may result in bleeding, due both to a deficiency of several coagulation factors and to an abnormality in the structure and function of fibrinogen, as well as thrombocytopenia due to hypersplenism.

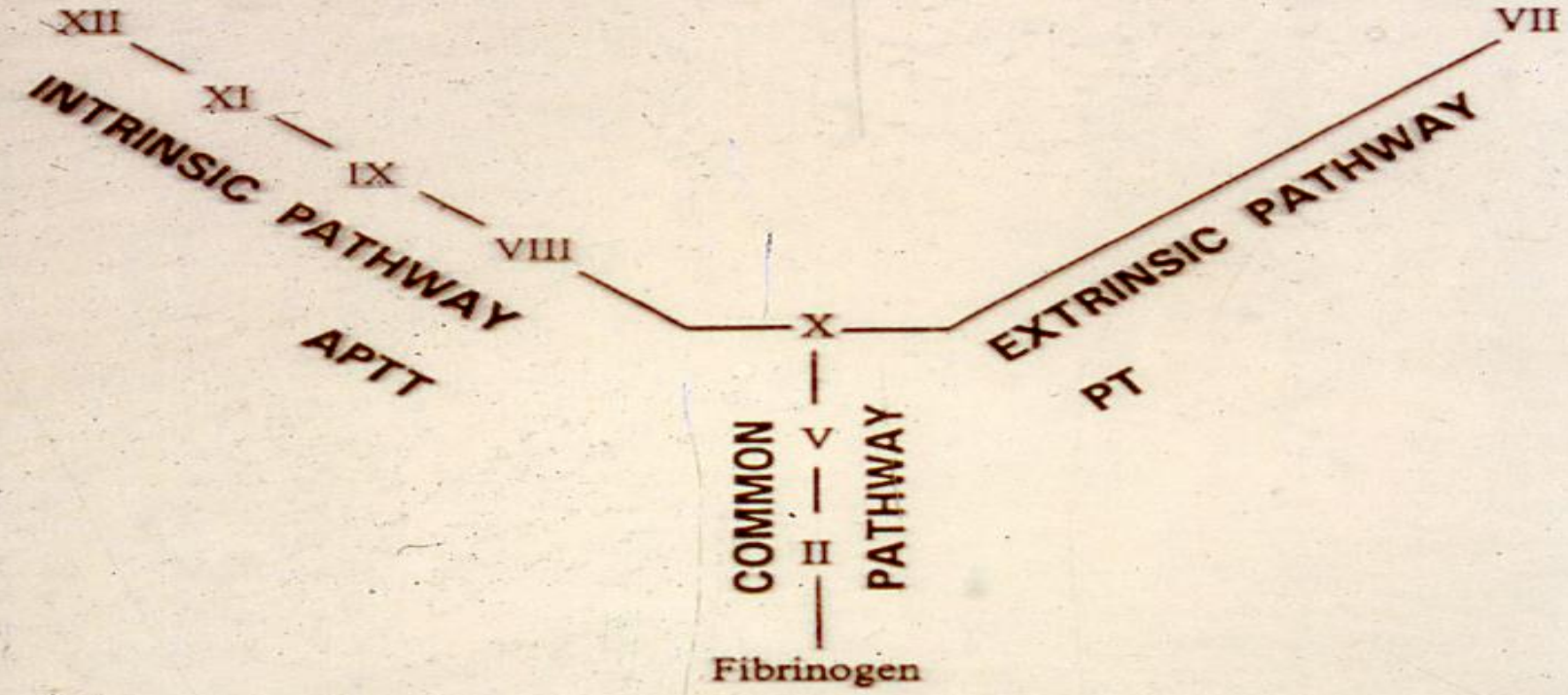
Haemophilia B (Factor IX deficiency, Christmas disease)

- The clinical features and inheritance of factor IX deficiency are identical to those in factor VIII deficiency. Factor IX deficiency affects about 1 in every 50,000 males (i.e. it is less frequent than factor VIII deficiency). The factor IX gene is located on the long arm of the X-chromosome, is much smaller than the factor VIII gene (containing eight exons).
- The APTT is prolonged and the PT normal. The diagnosis can be made by assay of the factor IX level. Plasma-derived factor IX concentrate or recombinant factor IX is available and should be administered intravenously as soon as spontaneous or post-traumatic bleeding starts. Factor IX has a longer half-life in the plasma (18-24 hours) than factor VIII and hence can be given at less frequent intervals.

THE COAGULATION CASCADE



INTERPRETATION OF RESULTS:



1. PT (Normal), APPT (Prolonged)
2. PT (Prolonged), APTT (Prolonged)
3. PT (Prolonged), APTT (Normal)
4. PT (Normal), APTT (Normal)

Genetics, prevalence and biochemistry

- Deficiency of factor VIII results from an abnormality in the factor VIII gene, which is very large (186 kilobases, 26 exons) and lies at the tip of the long arm of the X-chromosome.
- Ranging form single-point mutations to large deletions.
- Half of all severe cases are due to an inversion involving intron 22.
- The prevalence of this disorder is about one per 10 000 males.

cont'd…

- Females with haemophilia have been observed extremely rarely and these are either homozygotes for the abnormal gene or are heterozygotes in whom the normal X-chromosome has not produced sufficient quantities of factor VIII due to lyonization.
- The factor VIII molecule is a protein with a molecular weight of $8 X 10^4$ daltons. In the plasma, factor VIII is only found complexed with VWF, which acts as a carrier and prolongs its plasma half-life.

The Abnormalities in Von Willebrand Disease

- Abnormal bleeding time
- Prolonged APTT & normal PT
- Deficiency of Factor VIII Clotting activity
- Deficiency of Von Willebrand Factor (Ristocetin Co-factors)
- Low Von Willebrand Antigen
- Abnormal Platelet Aggregations

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PRINT FROM MEMORY

DATE: 5/24

COMMENTS: NORMAL PLATELETS

	SLOPE	AGG
1 ADP 2x10⁻⁶M	58	99%
2 ARACHIDONIC ACID	52	86%
3 COLLAGEN 1.9 mg/ml	62	89%
4 EPINEPHRINE 10⁻³M	30	95%

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

--- 1 MINUTE ---

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

--- 1 MINUTE ---

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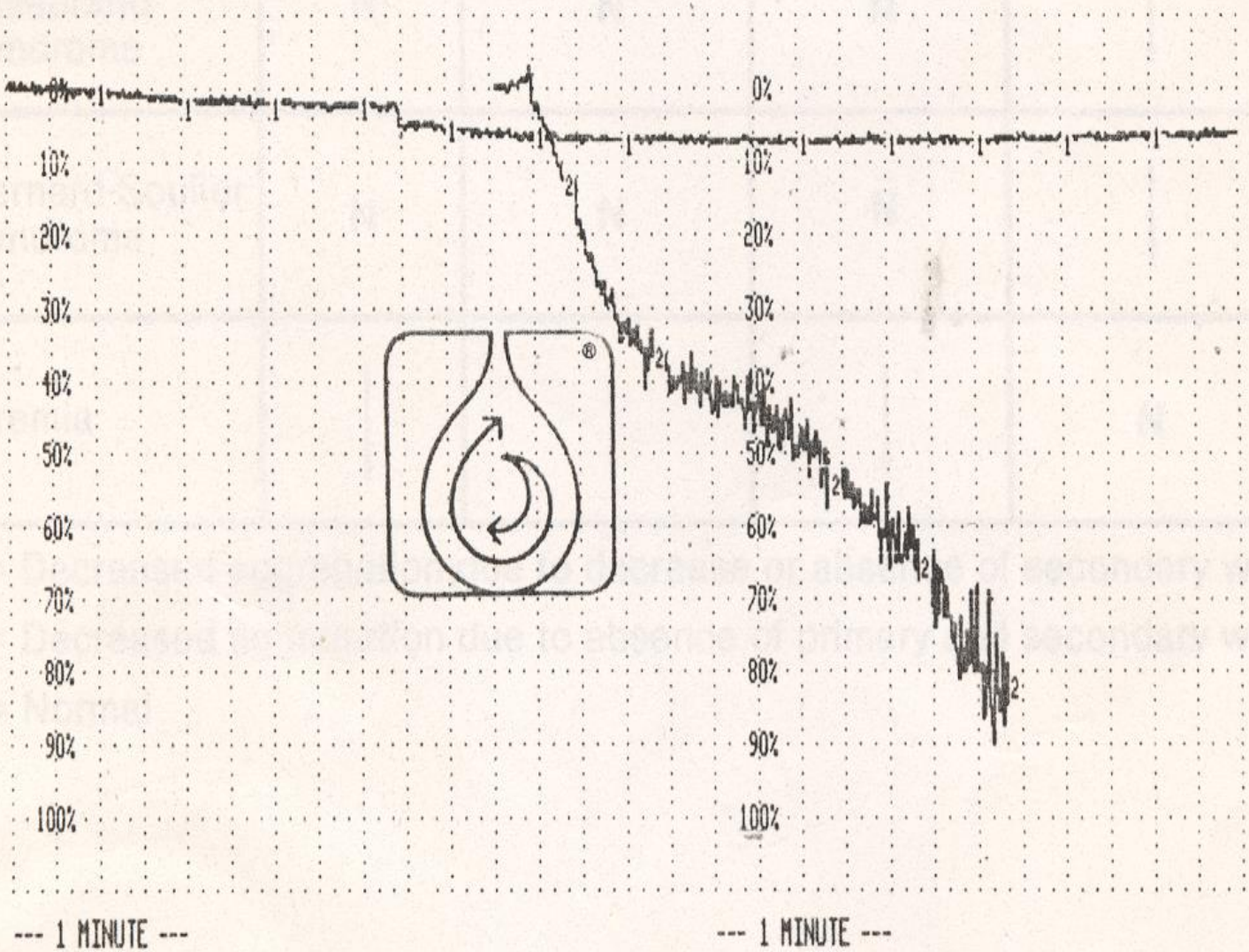

PRINT FROM MEMORY

DATE: 5/8/24

COMMENTS: Ristocetin, 1.25 mg/dL

	SLOPE	AGG
1 Non-diabetic patient	04	07%
2 Normal control	31	85%

Diagnosis of Haemophilia A & Von – Willebrand's

Haemophilia A	VW Disease
Bleeding time normal	Bleeding time abnormal
PT normal	PT normal
PTT abnormal	PTT abnormal
Factor VIII C ↓	Factor VIII C ↓
VWf : normal	vWf ↓
Factor VIII related antigen vWF antigen: normal	vWF antigen ↓
Ristocetin co-factor normal	Ristocetin co-factor low
Platelets aggregation normal	Platelets aggregation abnormal

Von Willebrand disease

- This is the most common inherited bleeding disorder, with a prevalence of up to 1%, although most mild cases are undiagnosed. It was described by von Willebrand in 1926 as occurring in several families on islands in the Baltic (Åland Islands). It is an autosomal disorder characterized by mild, moderate or severe bleeding. The bleeding results from either a qualitative abnormality or a deficiency of VWF. This factor is a protein with a molecular weight of 2.7×10^5 daltons and exists in the plasma as a variable-sized polymer, ranging from a dimer to a molecule containing 50-100 subunits. It has a dual function: first, it is an adhesive molecule that binds platelets to subendothelial tissues; second, it acts as a carrier for factor VIII. The reduction in VWF results in a reduction in factor VIII concentration (usually measured as clotting activity).

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- The gene for VWF is present on chromosome 12.
- Some defects result in a reduction in the plasma concentration of structurally normal VWF molecules, but others cause different qualitative abnormalities in the VWF molecule. VWD has been divided into three types: in types 1 (most frequent) and 3 there is a partial reduction or nearly complete absence of VWF molecules, respectively, and in type 2 there are qualitative abnormalities.
- Spontaneous bleeding is usually confined to mucous membranes and skin and takes the form of epistaxes and ecchymoses.
- Bleeding into joints and muscles is rare except in type 3 disease.

cont'd…

- The laboratory findings include a prolonged PFA closure time (if done), usually a prolonged APTT and reduced factor VIII clotting activity, reduced levels of VWF and impaired ristocetin-induced platelet aggregation; however, it is important to remember that the PFA and APTT may be within normal limits.
- For mildly or moderately affected patients with type 1 disease, desmopressin (DDAVP), which increases plasma levels of both VWF and factor VIII, should be tried before using blood products.
- Very high purity VWF may be used.
- The antifibrinolytic drug tranexamic acid may be used for treating epistaxis or menorrhagia and in combination with DDAVP or VWF-containing concentrates to manage dental extractions.

Treatment of Haemophilia A,B and Von Willbrand's Disease.

1. Local Measures

2. Replacement Therapy:
   a. Cryoprecipitate
   b. Factor VIII concentrate
   c. Factor IX concentrate for Haemophilia B
   d. Fresh frozen plasma for other factors deficiency
   e. DDAVP (1-deamino – 8D-arginine vasopressin) 0.3 mcg/kg. In mild haemophilia A and von willbrand's disease. Maximum of 3 doses with at least 8 hours between each dose.

Should be used with tranexamic acid 15 mg/kg I.V or oral 15 mg/kg 8 hourly.

3. Treatment of patients with inhibitors

4. Surgical and orthopoedic treatment.

5. Management of patients with hepatitis B, C chronic liver disease and HIV infections.

6. Liver transplant

Treatment of Haemophilia

1. Factor VIII replacement therapy
    a. Immunoaffinity –purified Factor VIII preparation
    Dose of Factor VIII to be infused (units) = weight (kg) x increment needed (u/dL)/2
    b. Reconbinant Factor VIII (five different commercial preapartions)

2. DDAVP (desmopressin) I.V or S.C or nasal spray

3. Local supportive measures

4. Prophylactic treatment
    - Factor VIII three time / week
    - Vascular access device such as Port-a-Catch if venous access is difficult

5. Social and psychological care

6. Multidisciplinary team management
    - Haematologist, Dental, Orthopaedic , Physiotherapist

7. Gene therapy.

Level of Factor VIII Desirable 15 mins. After the First Transfusion (IU/DL)

Lesion

Early haemarthroses Minor external bleeds	20-30 %
Dental Extractions Severe Haemarthroses Internal Haemorrhage	50-100 %
Major surgery Serious accidents	70-100 %

Formula for calculating the dose of factor

$$\frac{\text{Body weight kgs} \times \text{Desired \% rise of VIII}}{2} = \text{dose of factor VIII units every 8hrs/12hrs}$$

Treatment of Inhibitors

Development of inhibitors occurs in 5-10% of patients.

a. High dose Factor VIII

b. Recombinant activated Factor VII (VIIa)

c. Activated prothrombin complex concentrates
   - (FEIBA – Factor VIII inhibitor by passing activity).

d. Immunosuppresion with cyclosphosphamide and other agents

e. Intravenous immunoglobulin

f. High dose factor VIII

The New Classification of Von -Willebrand's Disease

Type 1. Partial quantitative deficiency of vWF.

Type 2. Qualitative deficiency of vWF.

2A. Decreased platelet dependent function associated with absent high molecular weight multimers of vWF.

2B. Variants with increased affinity for platelets Glyloprotein – 1b.

2M. As 2A but high molecular weight multimers of vWF present.

2N. Variants with decreased affinity for factor VIII.

Type 3. Virtually complete deficiency of vWF.

Classification of von Willebrand disease.

Type 1	Quantitative partial deficiency
Type 2	Functional abnormality
Type 3	Complete deficiency

Secondary classification of type 2 VWD

Subtype	Platelet-associated function	Factor VIII binding capacity	High MW VWF multimers
2A	Decreased	Normal	Absent
2B	Increased affinity for GPIb	Normal	Usually reduced/absent
2M	Decreased	Normal	Normal or ultra large
2N	Normal	Reduced	Normal

GPIb, glycoprotein Ib; MW, molecular weight; VWD, von Willebrand disease; VWF, von Willebrand factor.

Treatment of Von Willebrand Disease

a. Local measures

b. Antifibrinolytic agent (tranexamic acid for mild bleeding)

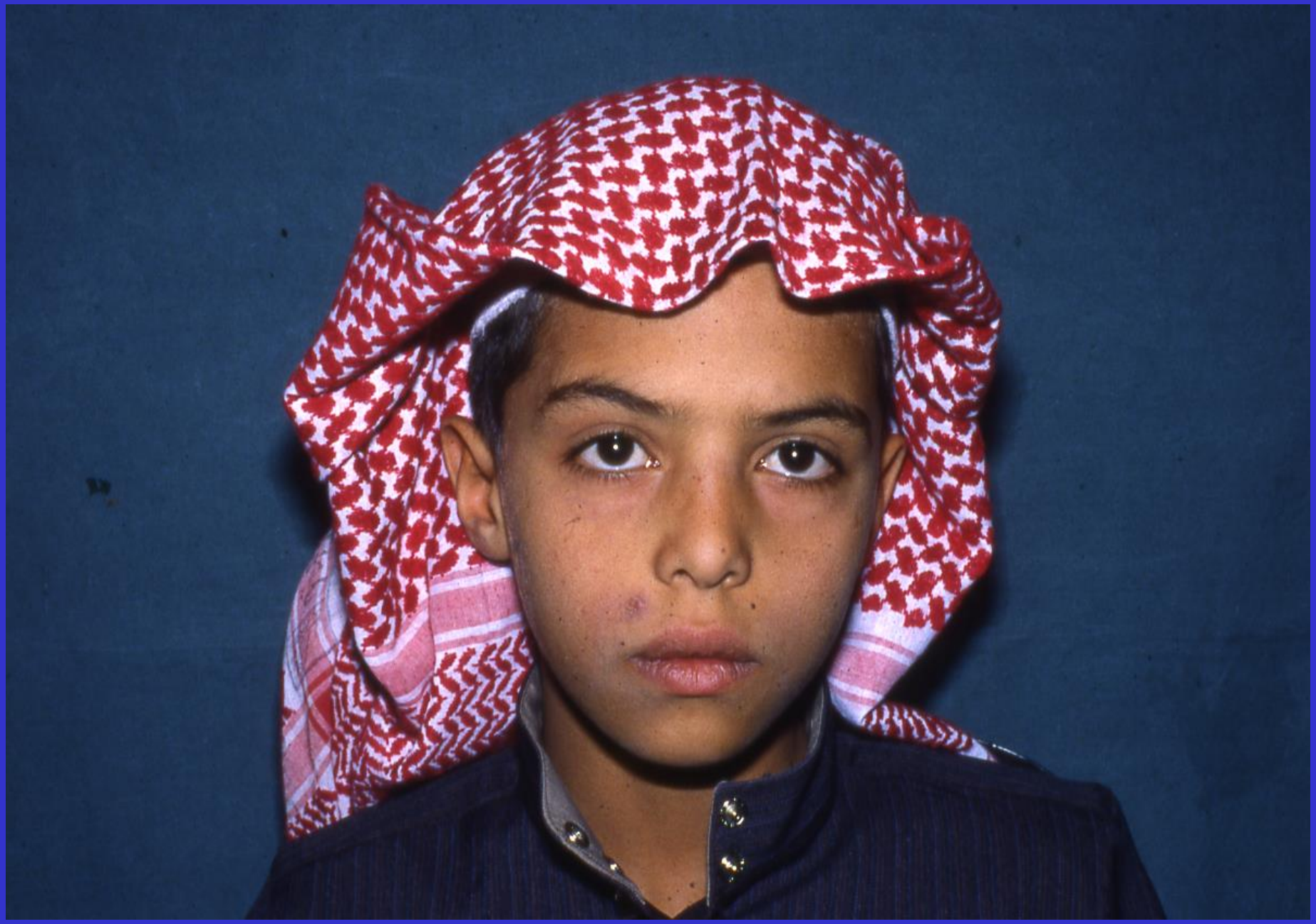
c. DDAVP infusion for type I VWD

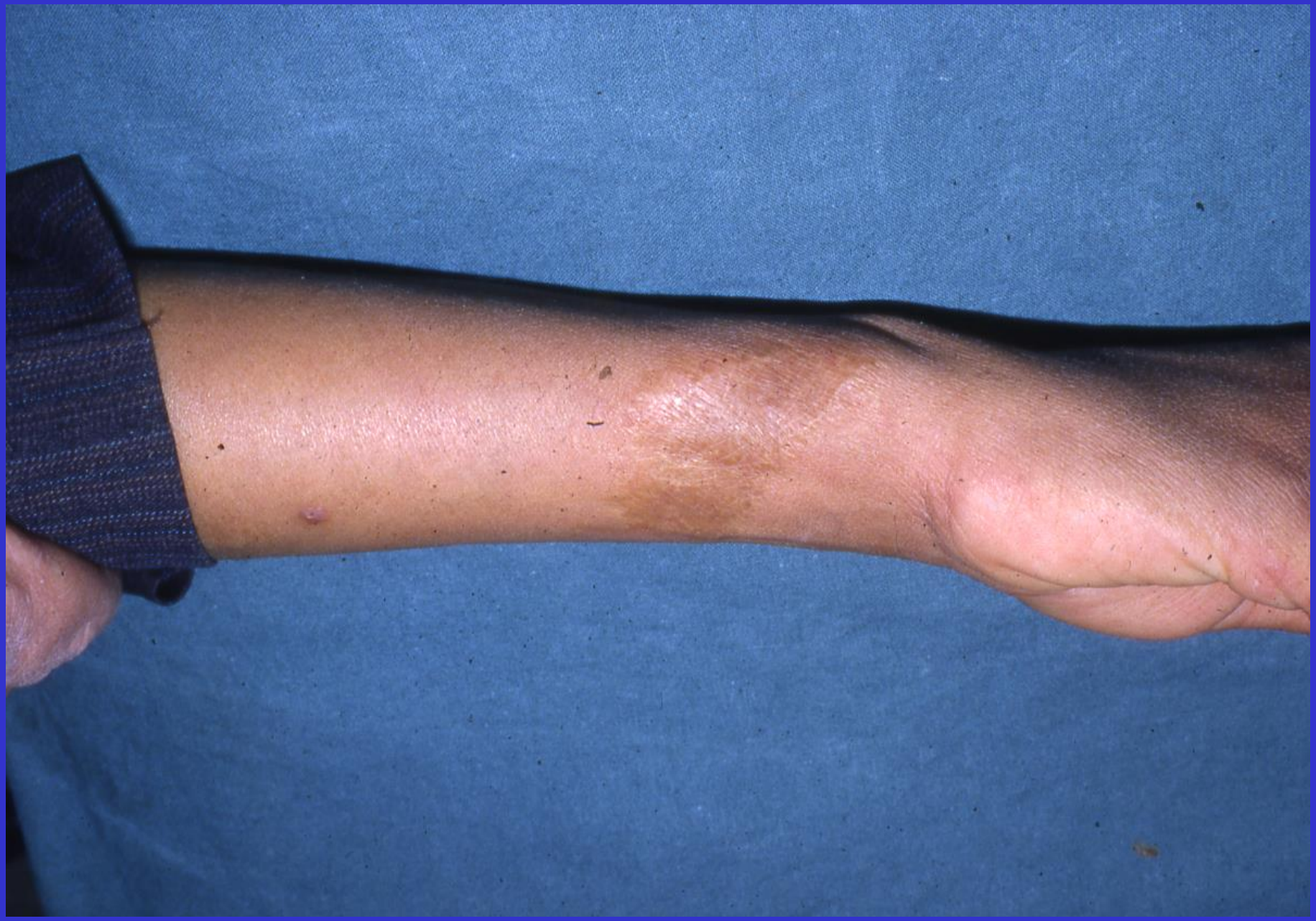
d. High purity factor VWF concentrates for patient with very low VWF levels
   - Factor VIII concentrate may also be given for more rapid correction.

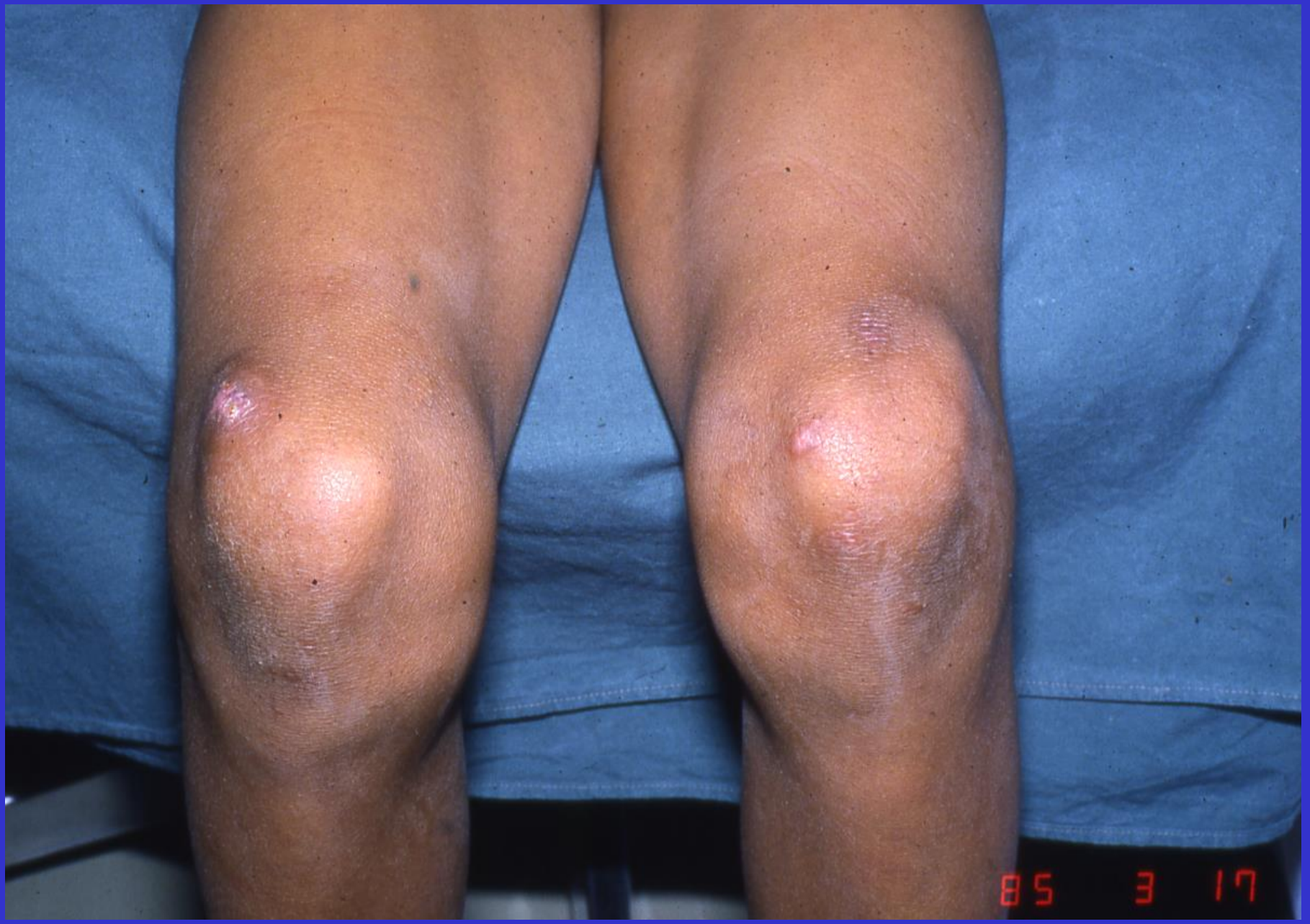
e. Social and psychological care.

FACTOR XIII DEFICIENCY

- Bruising with minor injury
- Hematoma after trauma
- Bleeding (secondary bleeding)
- Abnormal healing of wounds with excessive scar formation (keloid formation)



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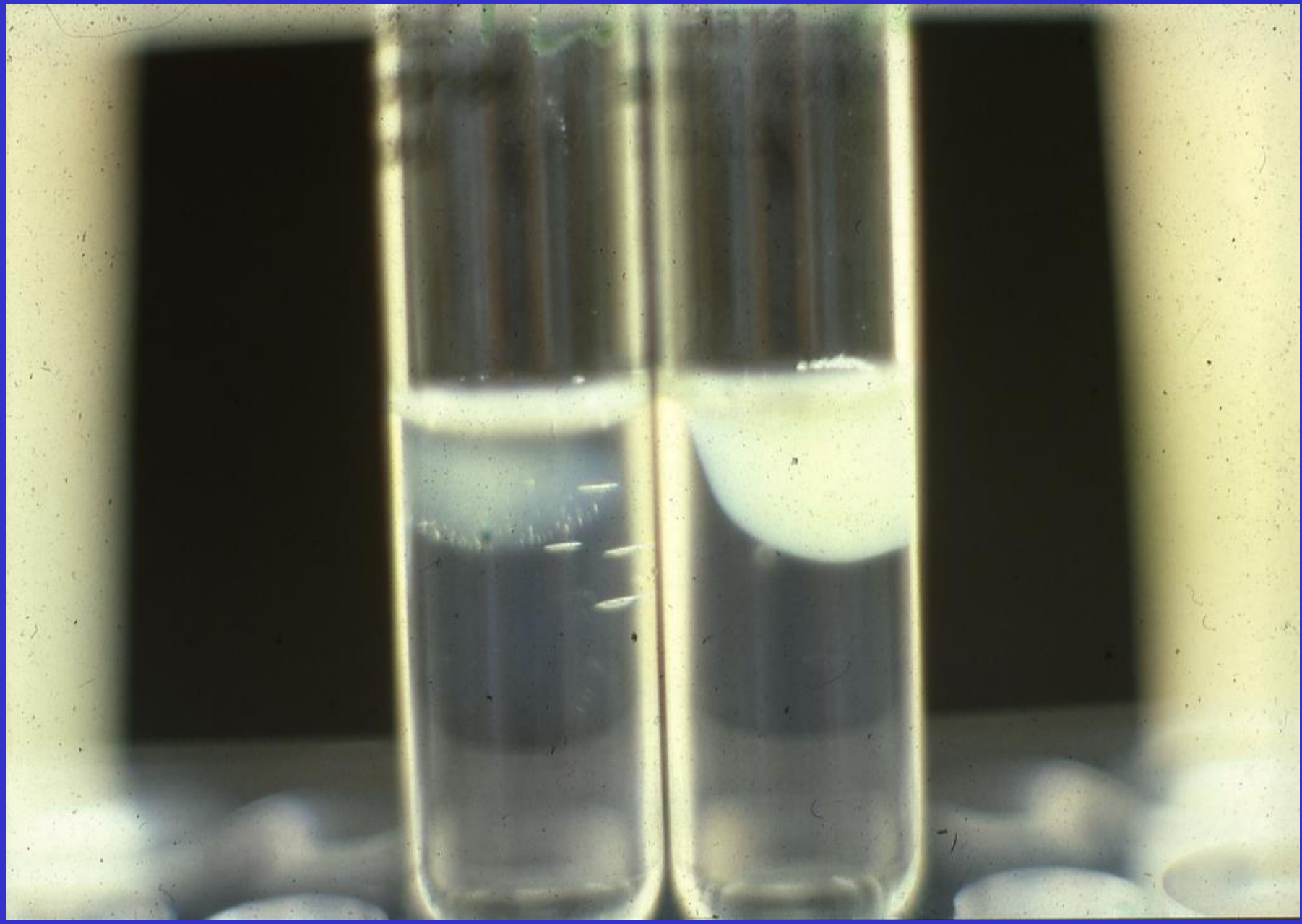
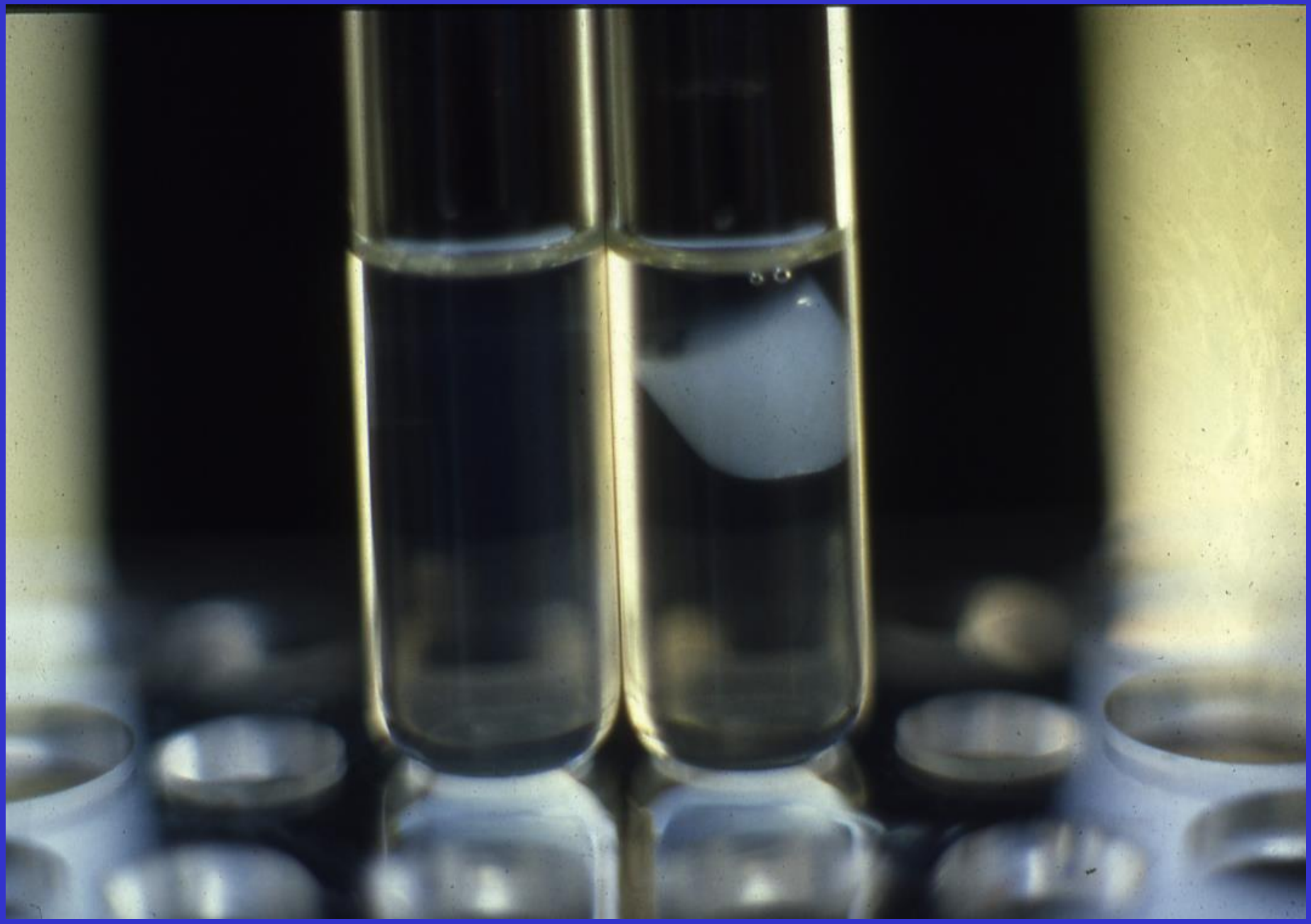




LABORATORY DIAGNOSIS OF FACTOR XIII DEFICIENCY

- Normal PT & Normal APTT
- Normal Bleeding time & Normal Platelet aggregation
- Normal fibrinogen level
- Abnormal clot stability with five molar urea
- Low Factor XIII level

ACQUIRED COAGULATION DISORDERS

DIC

DISSEMINATED INTRAVASCULAR COAGULATION

‘CONSUMPTION COAGULATIONPATHY’

‘DEFIBRINATION SYNDROME’

Causes of disseminated intravascular coagulation

- **Infections**

  Gram-negative and meningococcal septicaemia

  Clostridium welchii septicaemia

  Severe Falciparum malaria

  Viral infection – varicella, HIV, hepatitis, cytomegalovirus
- **Malignancy**

  Widespread mucin-secreting adenocarcinoma

  Acute promyelocytic leukaemia
- **Obstetric complications**

  Amniotic fluid embolism

  Premature separation of placenta

  Septic abortion

Causes of disseminated intravascular coagulation *(cont'd…)*

***Hypersensitivity reactions**

Anaphylaxix

Incompatible blood transfusion

***Widespread tissue damage**

Following surgery or trauma

After severe burns

***Vascular abnormalities**

Kasabach-Merritt syndrome

Leaking prosthetic valves

Cardiac bypass surgery

***Miscellaneous**

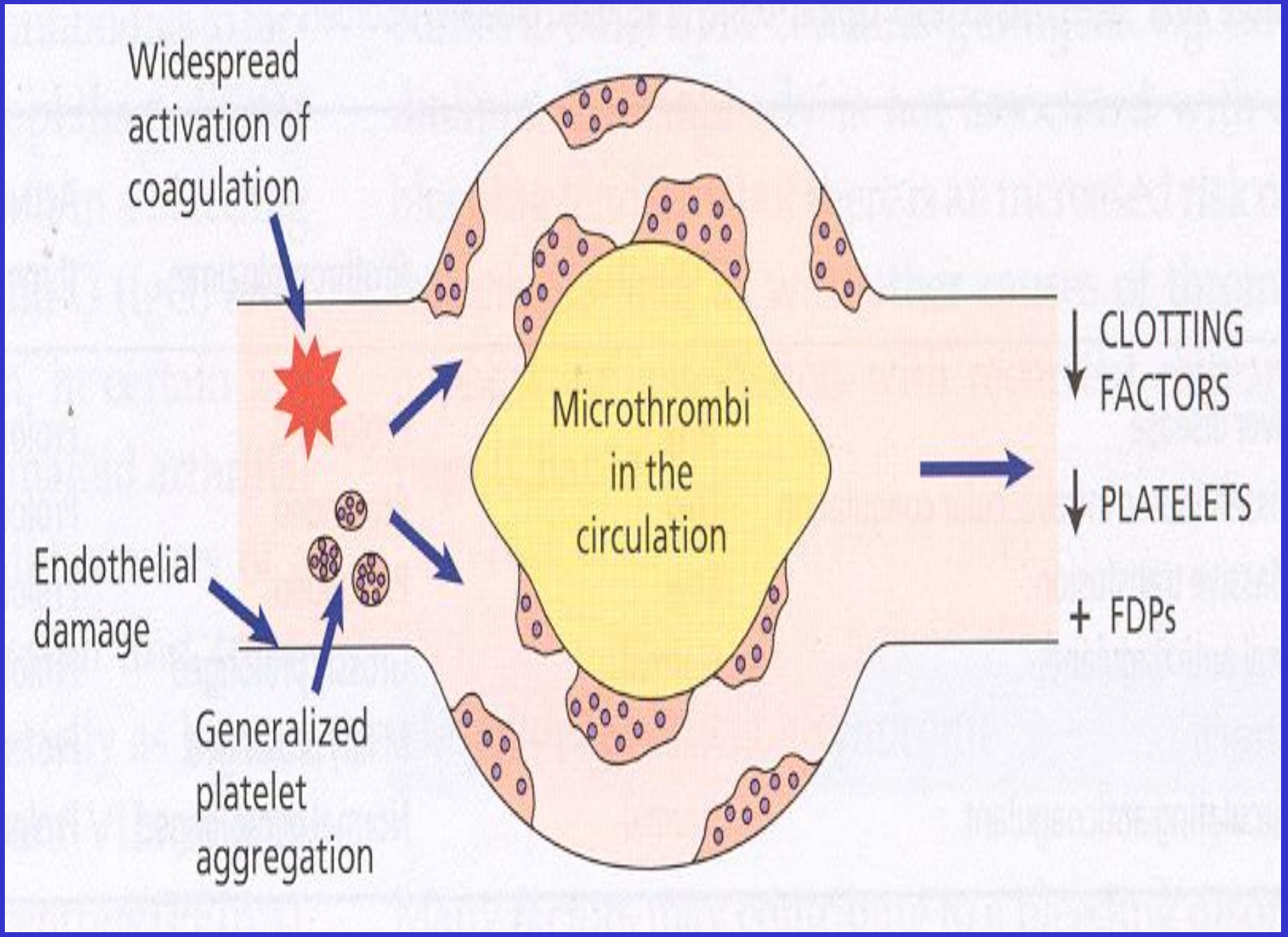
Liver failure

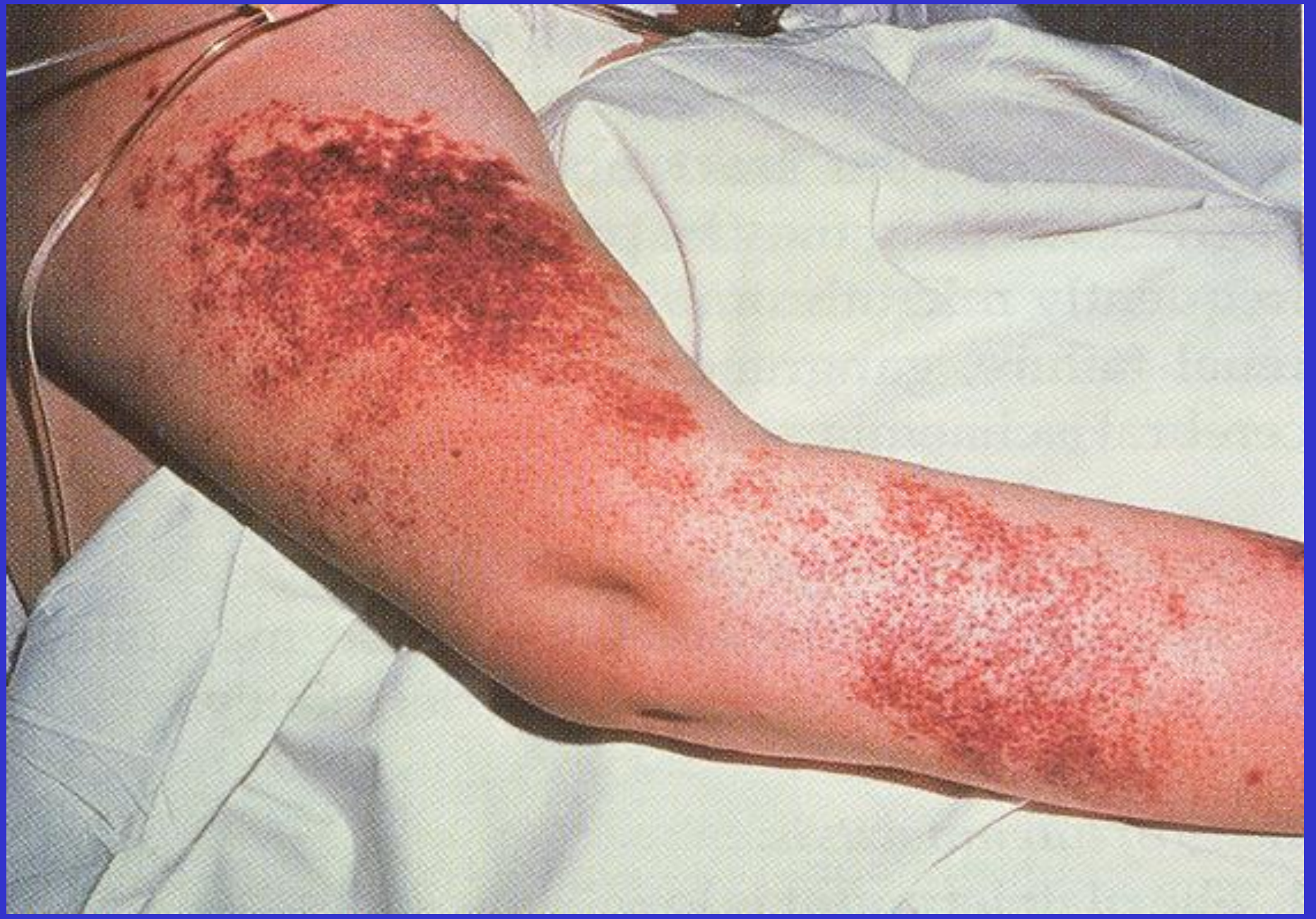
Snake and invertebrate venoms

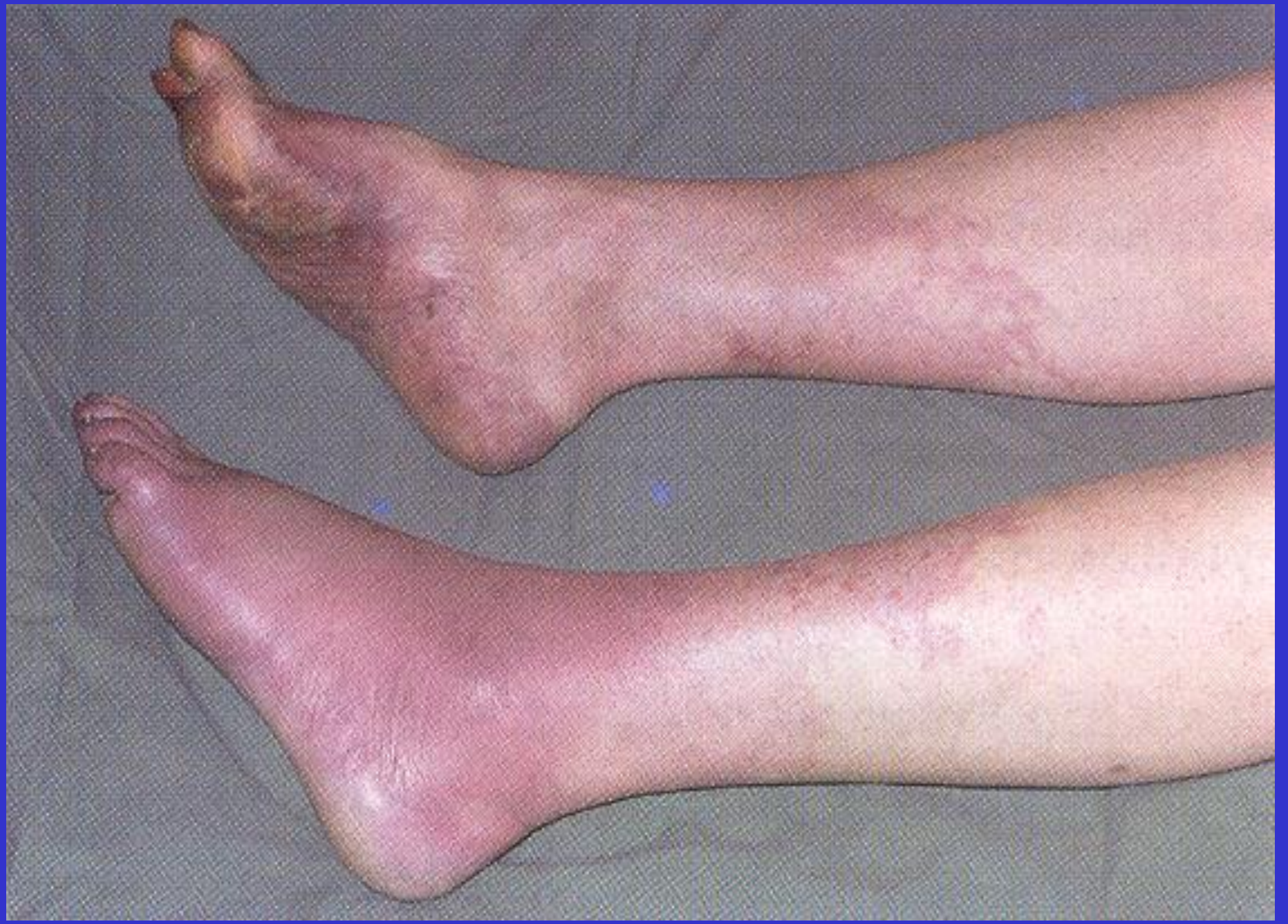
Hypothermia

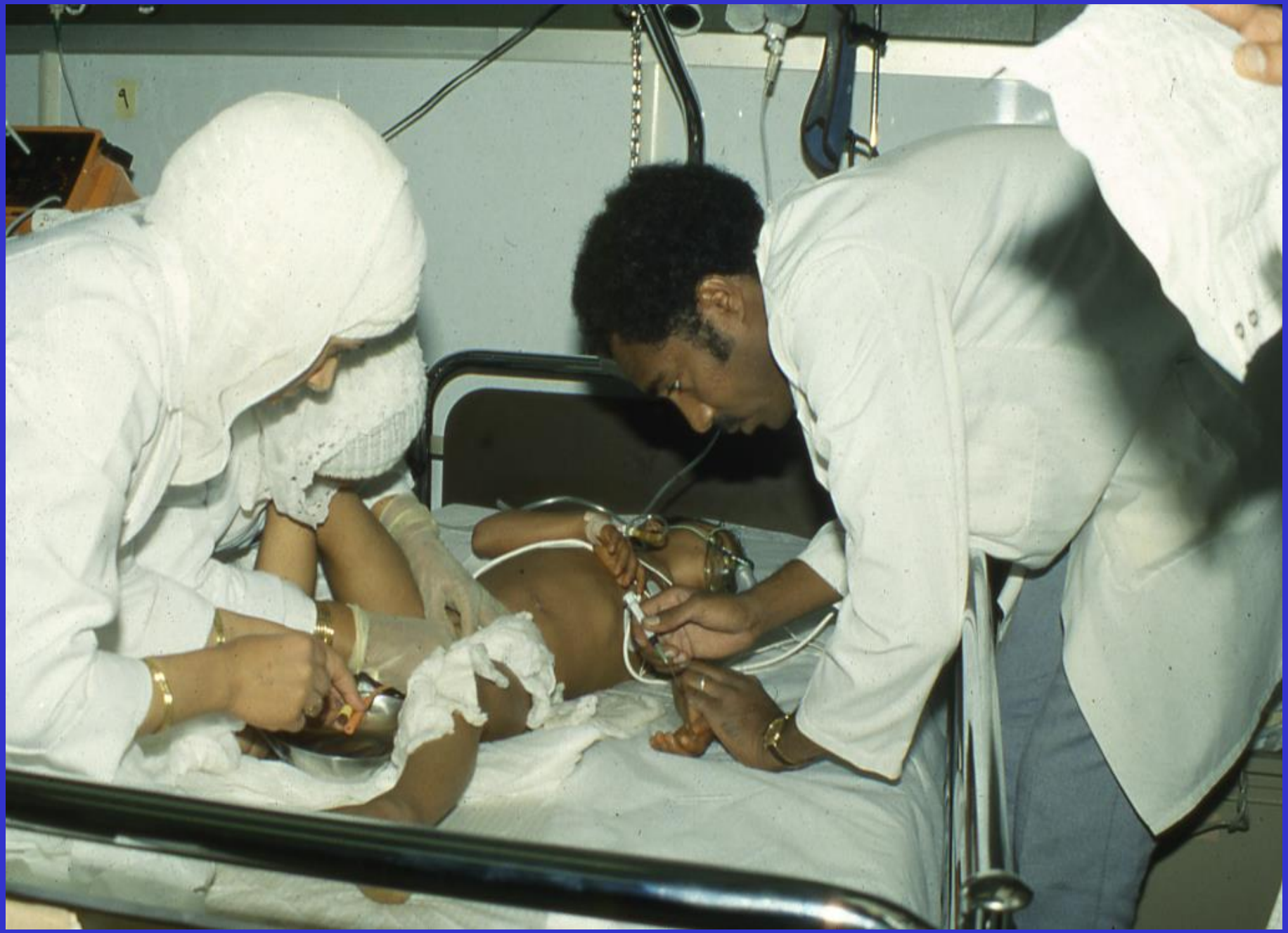
Heat stroke

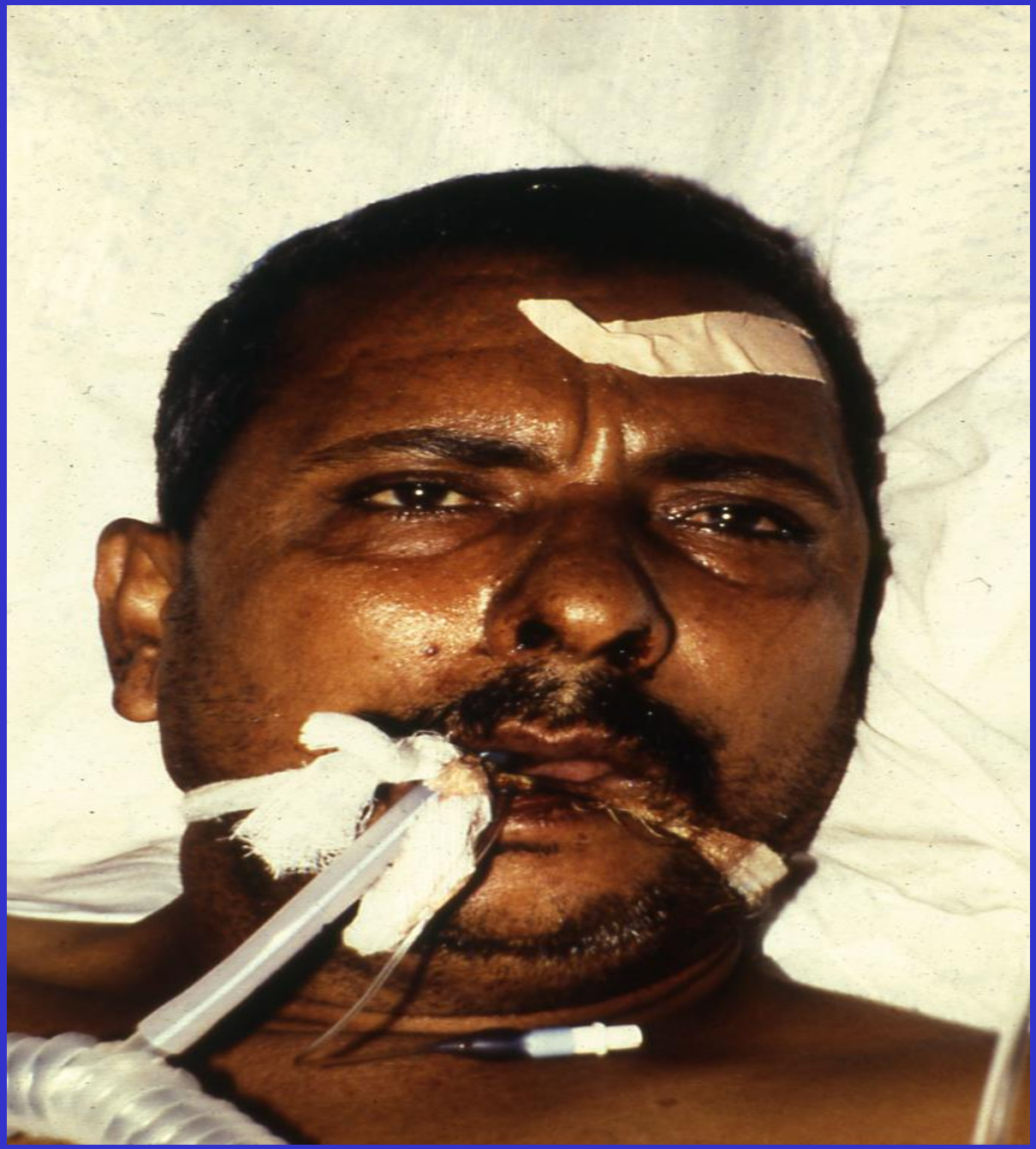
Acute hypoxia

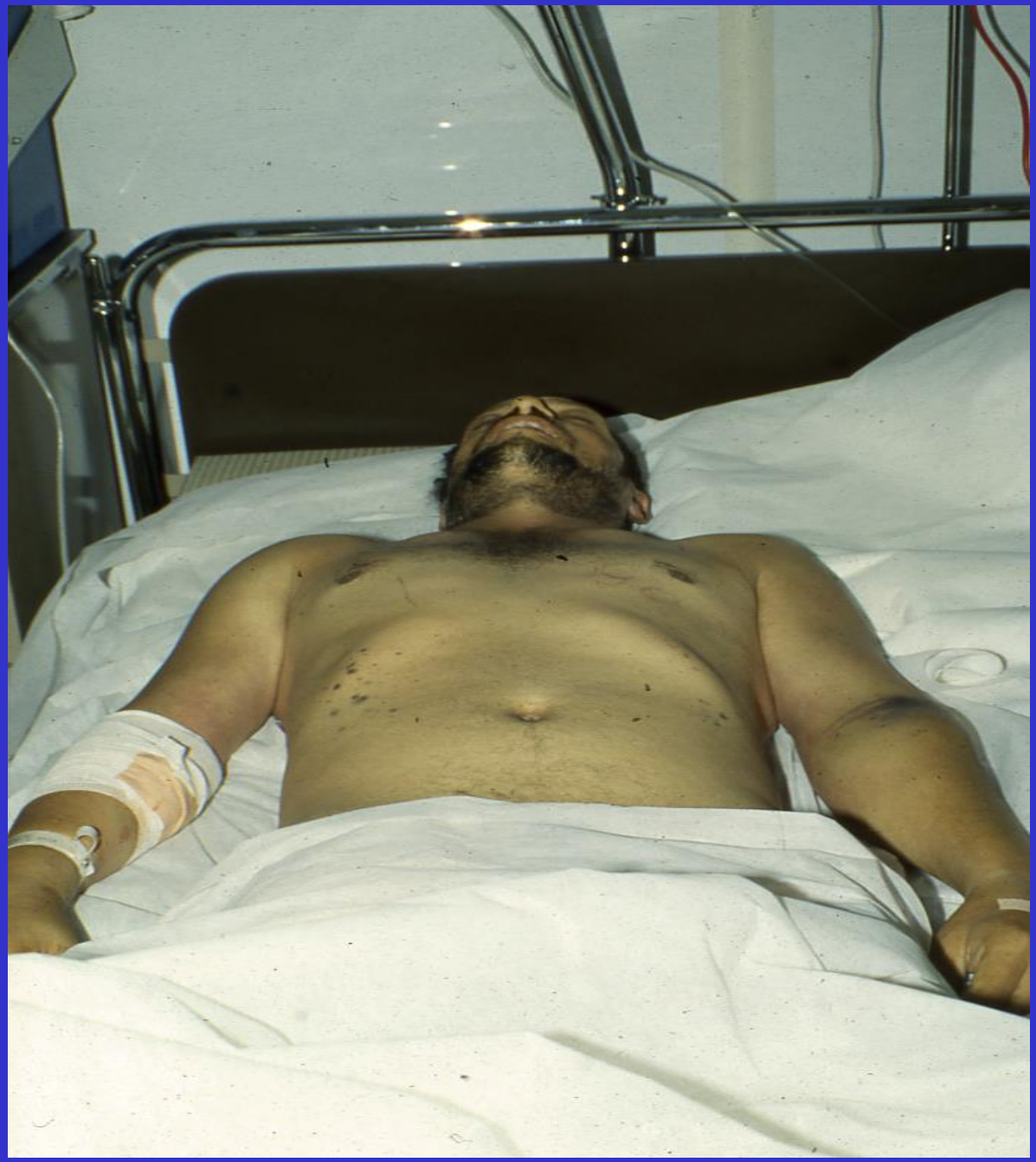

Widespread activation of coagulation
Endothelial damage
Generalized platelet aggregation
Microthrombi in the circulation
CLOTTING FACTORS
PLATELETS
+ FDPs

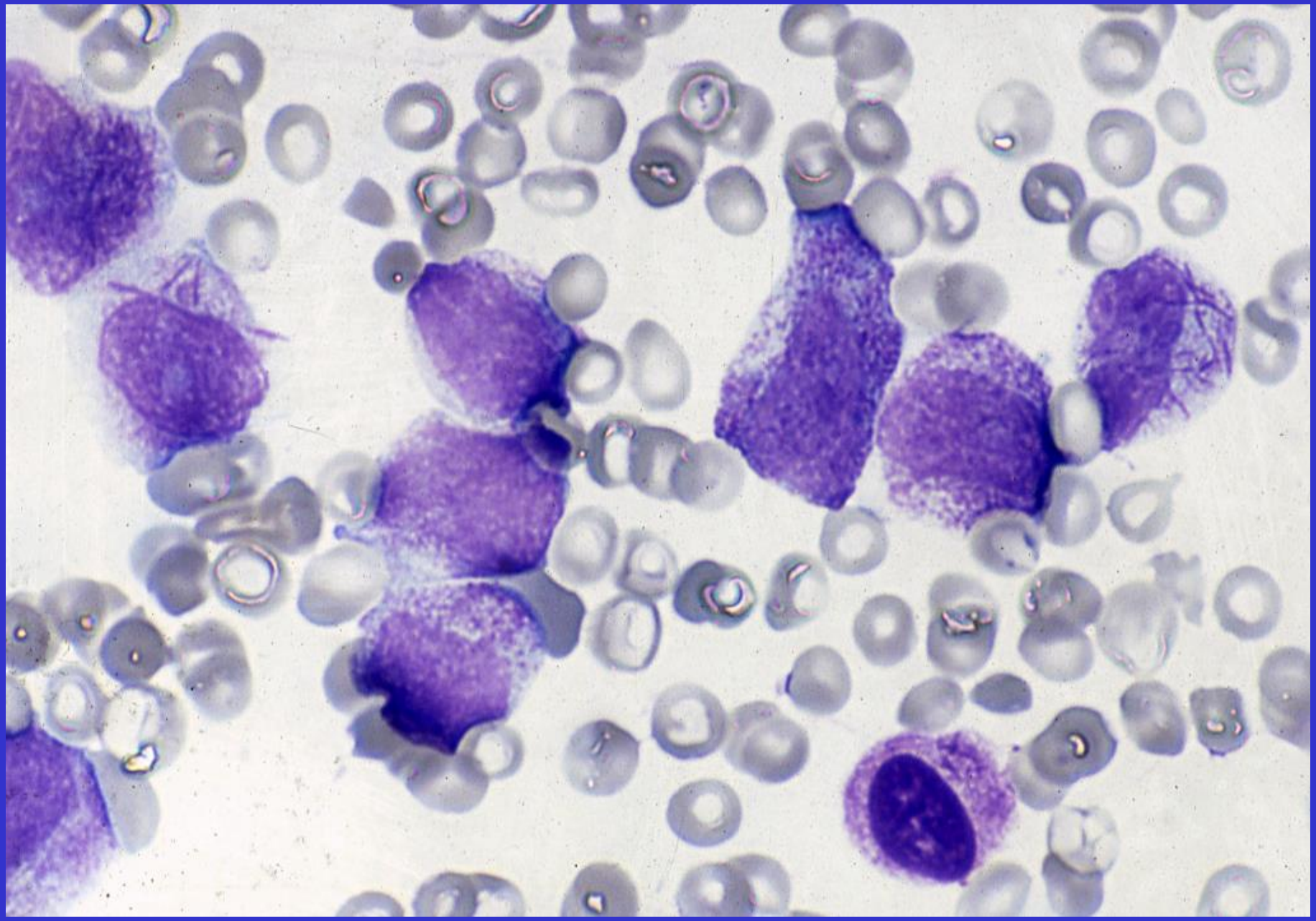


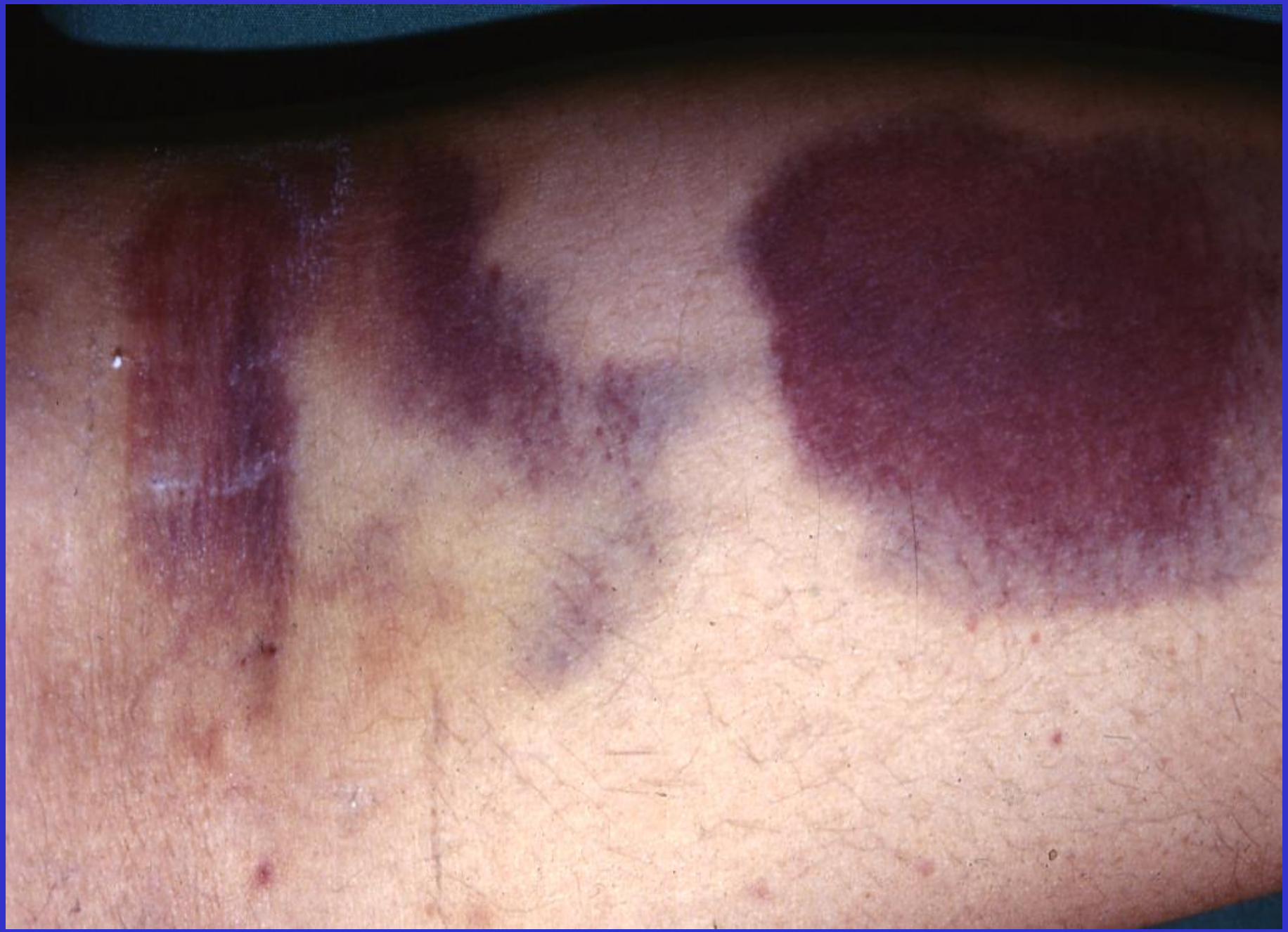












Disseminated intravascular coagulation (DIC)

- DIC describes a process in which there is a generalized activation of the clotting system followed by marked activation of the fibrinolytic system.
- Acute DIC may be associated with premature separation of the placenta, amniotic fluid embolism or shock, and may also be seen in certain bacterial infections such as meningococcal septicaemia.
- It is a common complication following intravascular haemolysis of red cells after a mismatched transfusion.

cont'd…

- Chronic DIC is seen when there is retention of a dead fetus as well as in patients with disseminated carcinoma, lymphoma and leukaemia (especially acute promyelocytic leukaemia).
- Clotting cascade may be activated in various ways; namely:

1) by the release of TF from damaged tissues
2) by damage to endothelial cells
3) by abnormal activators of coagulation

cont'd…

- Activation of the cascade leads to the generation and dissemination of large amounts of thrombin in the circulation, the activation of platelets and the formation of intravascular microthrombi.
- As a consequence of the fibrin formation, the fibrinolytic mechanism is activated, resulting in high concentrations of FDPs, including D-dimers. This leads to further haemostatic impairment, since FDPs inhibit fibrin clot formation by interfering with the polymerization of the fibrin monomer. FDPs also interfere with the aggregation of platelets.

cont'd…

- The haemorrhagic manifestations may be so severe in acute DIC as to lead to death
- In chronic DIC, the haemorrhagic tendency may be mild or moderate. However, some patients with chronic DIC are asymptomatic because the activation of the clotting and fibrinolytic systems is finely balanced and the production of clotting factors and platelets is sufficiently increased to compensate for their increased consumption.

Diagnosis

The investigations of value in the diagnosis of acute or chronic DIC are as follows:

- *The platelet count*: Platelets become enmeshed in the fibrin clots on the vascular endothelium and thrombocytopenia is an early and common sign.
- *The APTT and the PT*: These are usually prolonged, due to the depletion of clotting factors, especially in acute DIC.
- *The fibrinogen concentration*: This is reduced.

cont'd…

- *The thrombin time*: This may be prolonged due to a combination of a low fibrinogen and excessive amounts of FDPs.
- *Estimation of FDPs using the D-dimer assay*: FDPs including D-dimers are increased. D-dimers can be detected by rapid immunological tests in which latex particles coated with monoclonal antibody directed against D-dimer are agglutinated by D-dimers present in plasma.

Treatment

- Treatment is aimed at preventing further coagulation by removal of the initiating cause.
- Supported with transfusions of blood, fresh-frozen plasma and platelet concentrates in order to restore blood volume and replace clotting factors and platelets.

Acquired haemophilia

A rare but devastating acquired bleeding disorder is due to autoantibody-mediated factor VIII deficiency. It can occur in either sex, is more common in the elderly and has a high mortality. It is treated with ‘bypassing agents’ such as recombinant factor VIIa or FEIBA and immune suppression.

Anticoagulant drugs

The two most frequently used anticoagulant drugs are heparin and vitamin K antagonists such as warfarin. Parenteral heparin is used in patients with deep vein thrombosis (DVT) or pulmonary embolism (PE) and is followed by oral warfarin therapy. Subcutaneous heparin is used to reduce the risk of DVT and PE in hospitalized patients, including those undergoing surgery (especially hip surgery). Heparin does not cross the placenta and is therefore the preferred drug when anticoagulation is required during pregnancy. The oral anticoagulant warfarin is administered initially for three months to patients with DVT or PE and may be indicated long term to prevent recurrent venous thrombosis. Long-term warfarin is also used after the insertion of mechanical heart valves and in patients with atrial fibrillation.

Heparin

- Standard unfractionated heparin is an acidic mucopolysaccharide (average molecular weight 1.5 *X* 10^4 daltons) that has to be administered intravenously or subcutaneously. When administered intravenously, its biological half-life is 1 h. Heparin potentiates the action of AT, a molecule that inactivates the activated serine protease coagulation factors thrombin (IIa) and Xa.

cont'd…

- Low molecular weight heparin (average molecular weight 4-5 *X* 10^3 daltons) is used subcutaneously, it inactivates Xa to a greater extent than IIa and has a longer biological half-life. Examples of low molecular weight heparins currently in use are dalteparin, enoxaparin and tinzaparin. Fondaparinux is a synthetic pentasaccharide that induces AT specifically to inhibit Xa.

cont'd…

- For the treatment of thrombosis or embolism, standard heparin may be administered as a bolus of 5000 units (70 units/kg) intravenously, followed by a continuous intravenous infusion of 15-25 units/kg/h. Treatment is monitored by performing the APTT, the heparin dosage being altered so as to maintain the APTT at 1.5-2.5 times the normal value. The treatment of choice is now low molecular weight heparin given subcutaneously once a day with no monitoring.

cont'd…

- Haemorrhage due to overdosage is managed by stopping the heparin and, if necessary, by giving protamine sulphate intravenously. Side effects of heparin include heparin-induced thrombocytopenia (HIT) via an antibody-based mechanism, osteoporosis (following long-term use), alopecia and hypersensitivity reactions.

Warfarin sodium

- This is a coumarin derivative that is administered orally once a day. It is a vitamin K antagonist and interferes with the carboxylation and hence with the functional activity of factors II, VII, IX and X, protein C and protein S. After the first dose, clotting factor activity is reduced in the order VII, IX, X and II.
- It is customary to prescribe 5 or 10 mg warfarin on the first day and subsequent doses are based on the INR. The therapeutic range for the INR is usually 2-3. A higher range of 3-4 is used for recurrent DVT or PE, despite an INR >2 and for patients with certain prosthetic heart valves.

cont'd…

- Bleeding is controlled by stopping the warfarin by administering vitamin K and, if necessary, administering prothrombin complex concentrates.
- Warfarin crosses the placenta and may cause developmental abnormalities such as chondrodysplasia, microcephaly and blindness. It is therefore contraindicated in the first trimester of pregnancy. It should also not be administered during the last few weeks of pregnancy because of its anticoagulant effect on the fetus and the consequent risk of fetal or placental haemorrhage.

Direct oral thrombin inhibitors and direct oral Xa inhibitors

Drugs that directly inhibit thrombin (e.g. dabigatran etexilate) or Xa (e.g. rivaroxaban, apixaban, edoxaban) have been developed as oral anticoagulants that offer an alternative to warfarin in the treatment of venous thromboembolism and atrial fibrillation. They can be given in fixed dose without monitoring; they have relatively short half-lives (in the order of 9-17 hours) but no antidote.

Investigation of a patient with abnormal bleeding

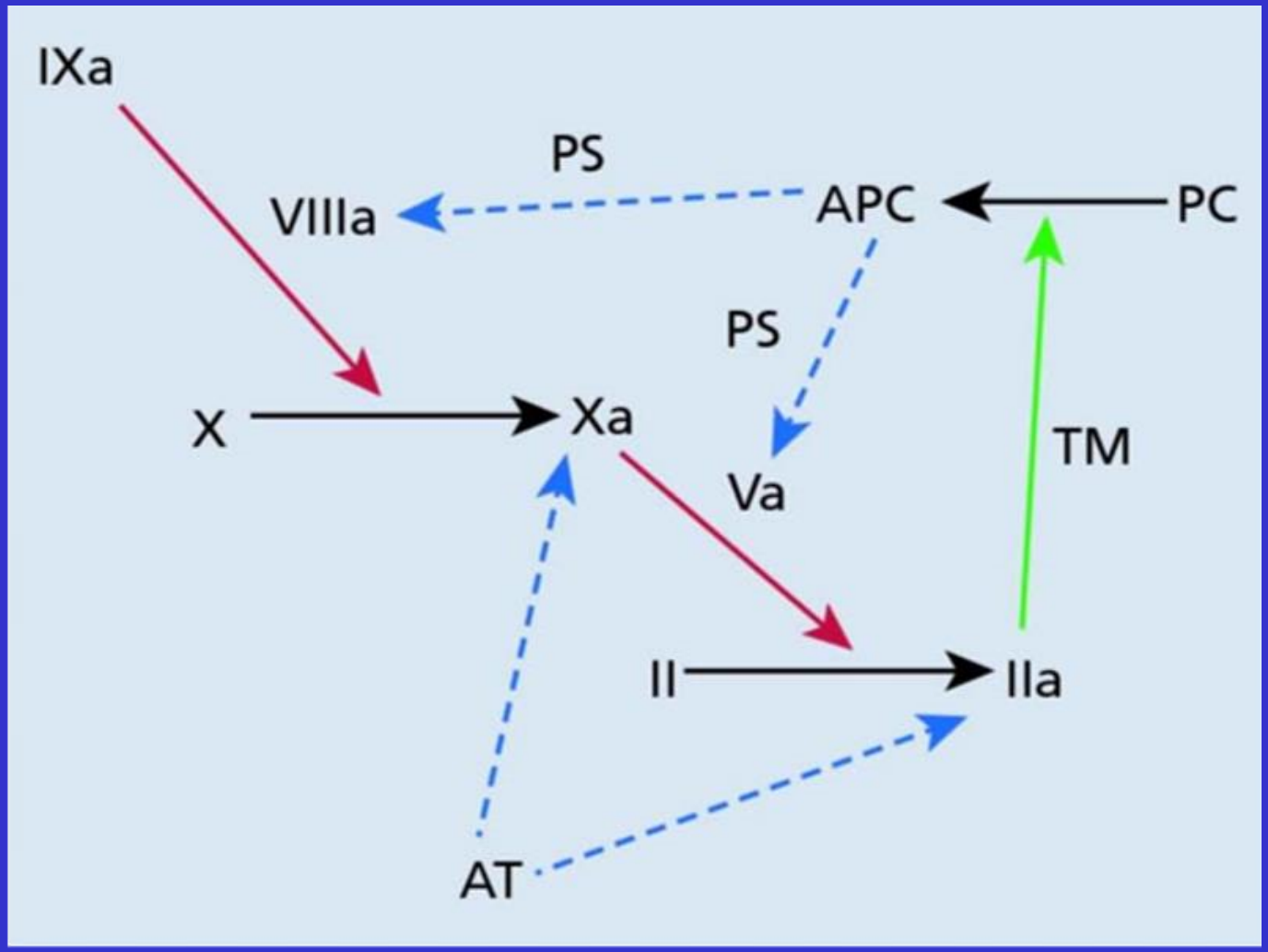
- A most important step in the diagnostic process is taking a good history from the patient.
- The screening tests that are useful in investigating a patient who gives a history of excessive bleeding are the following:
  - A blood count, including a platelet count, and examination of a blood film.
  - The prothrombin time and the activated partial thromboplastin time.
  - The thrombin time or fibrinogen assay.

cont'd…

- The PFA 100 can be used as a screening test for abnormal platelet function and platelet aggregation studies. If any of these tests is found to be abnormal, further specialized tests may be necessary.

Natural anticoagulant mechanisms and the prothrombotic state (thrombophilia)

There are natural anticoagulant mechanisms in the plasma that prevent localized fibrin formation from becoming widespread. The most important molecules involved in these mechanisms are AT, protein C and protein S, all of which are produced in the liver. Inherited or acquired abnormalities of these inhibitors of coagulation may lead to a prothrombotic state (thrombophilia).



The natural anticoagulants.

The antiphospholipid syndrome

- The antiphospholipid antibody syndrome is defined by the presence of antiphospholipid antibodies (either anticardiolipin antibodies, antibeta-2 glycoprotein I antibodies or lupus anticoagulant) associated with thrombosis or certain problems in pregnancy. Lupus anticoagulant prolongs the results of coagulation tests that depend on phospholipid (e.g. the APTT).

cont'd…

- Features of the antiphospholipid syndrome may include recurrent venous thromboses, recurrent arterial thrombosis (most commonly stroke) and recurrent miscarriage (due to placental thrombosis and infarction). Thrombocytopenia is common. Antiphospholipid antibodies are found in some patients with SLE or other autoimmune disorders as well as in individuals with no other evidence of an immunological abnormality.

LABORATORY ASPECTS OF HEMATOLOGY COAGULATION.

TEST CARRIED OUT ARE:

1. PROTHROMBIN TIME (PT)
2. ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT)
3. PLASMA FIBRINOGEN
4. CAOGULATION FACTOR ASSAYS
5. PLASMA FIBRIN / FIBRINOGEN DEGRADATION PRODUCTS(FDP'S) AND D.DIMERS.

METHODS USED ARE:

1- AUTOMATIC

2-MANUAL

LABORATORY TEST USED IN DIAGNOSIS OF COAGULATION DISORDERS

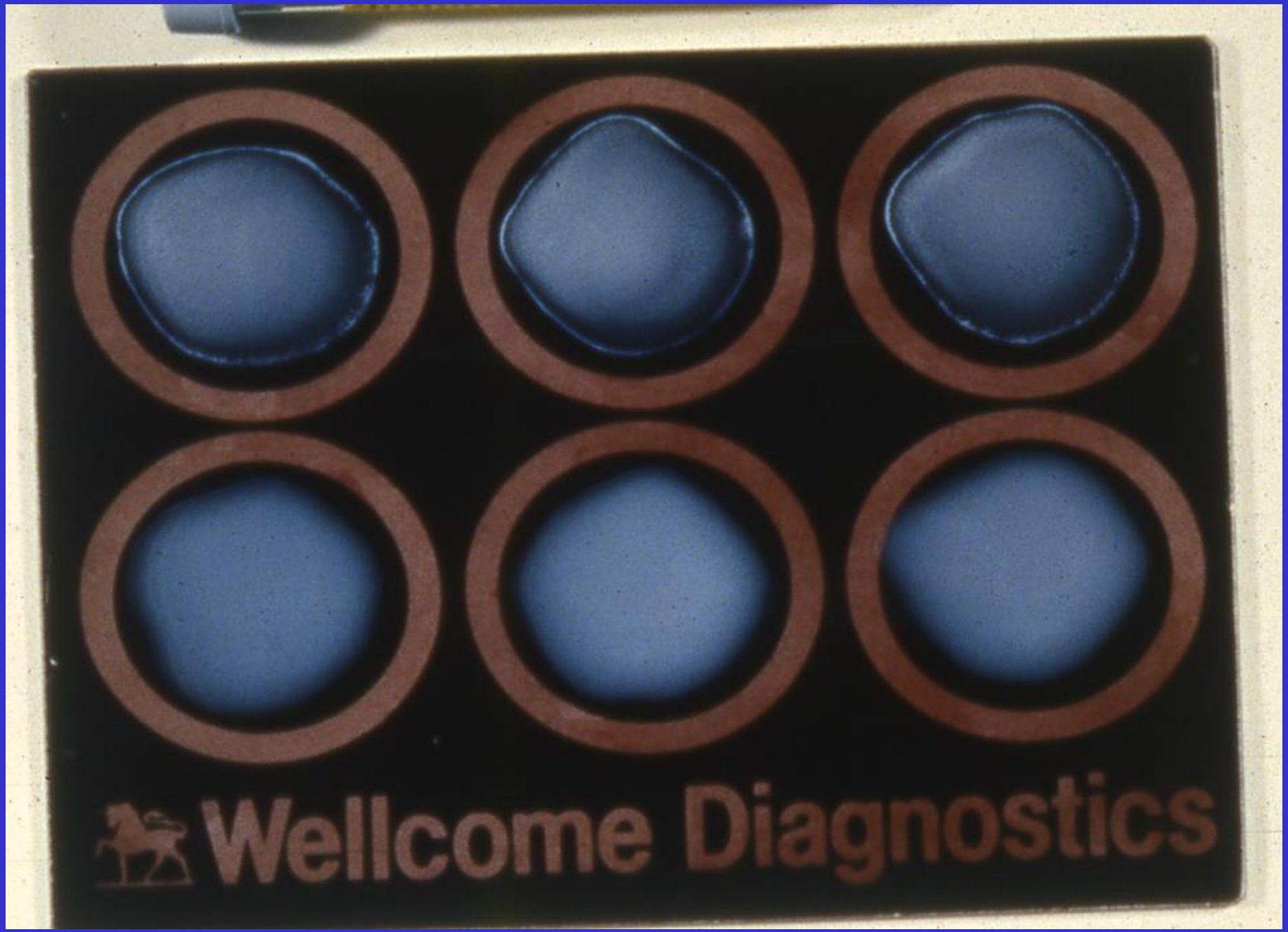
A. SCREENING TESTS	NORMAL
PROTHROMBIN TIME (PT)	10-14 SEC.
TEST EXTRINSIC &COMMON PATHWAYS	
ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT&PTTK)	30-40SEC.
TESTS INTRINSIC&COMMON PATH WAYS	
THROMBIN TIME (TT)	10-12SEC.
TESTS FIBRINOGEN- FIBRIN CONVERSION	

B. SPECIFIC FACTORS ASSAYS

C. TESTS OF FIBRINOLSIS

EUGLOBULIN CLOTIYSIS TIME

FIBRIN DEGRADATION PRODUCTS(FDPS)


Wellcome Diagnostics

Haemostasis tests: typical results in acquired bleeding disorders

	Platelet count	Prothrombin time	Activated partial thromboplastin time	Thrombin time
Liver disease	Low	Prolonged	Prolonged	Normal (rarely prolonged)
Disseminated intravascular coagulation	Low	Prolonged	Prolonged	Grossly prolonged
Massive transfusion	Low	Prolonged	Prolonged	Normal
Oral anticoagulants	Normal	Grossly prolonged	Prolonged	Normal
Heparin	Normal (rarely low)	Mildly prolonged	Prolonged	Prolonged
Circulating anticoagulant	Normal	Normal or prolonged	Prolonged	

Screening Tests of Hemostasis

Screening tests	Defects
B.T. Prolonged	Platelets (↓ or dysfunction) + Von Willebrand's disease
APTT prolonged	Factors: XII, XI, VIII, IX, X, V, II, I
P.T. Prolonged	Factors: VII, X, V, II, I
T.T. Prolonged	Fibrinogen (Factor I) high FDPS
Reptilase time prolonged	Fibrinogen (factor I) high FDPS. Not effected by Heparin therapy
FDPS high	▪ D.I.C. ▪ Snake Bite ▪ Thrombolytic therapy ▪ Dysfibrinogenemia
Platelet Count Low	Thrombocytopenia
Platelet Count Normal	Platelet dysfunction

Indications for the use of fresh frozen plasma

- Coagulation factor deficiency (where specific or combined factor concentrate is not available)
- Reversal of warfarin effect.
- Multiple coagulation defects, e.g. in patients with liver disease, DIC
- Massive blood transfusion with coagulopathy and clinical bleeding
- Thrombotic thrombocytopenic purpura
- Deficiencies of antithrombin, protein C or protein S
- Some patients with immunedeficiency syndromes

Oral Anticoagulants Indications

- Venous thrombosis and pulmonary embolism.
- Atrial fibrillation.
- Heart valve prostheses.
- Myocardial infarction (Selected cases)

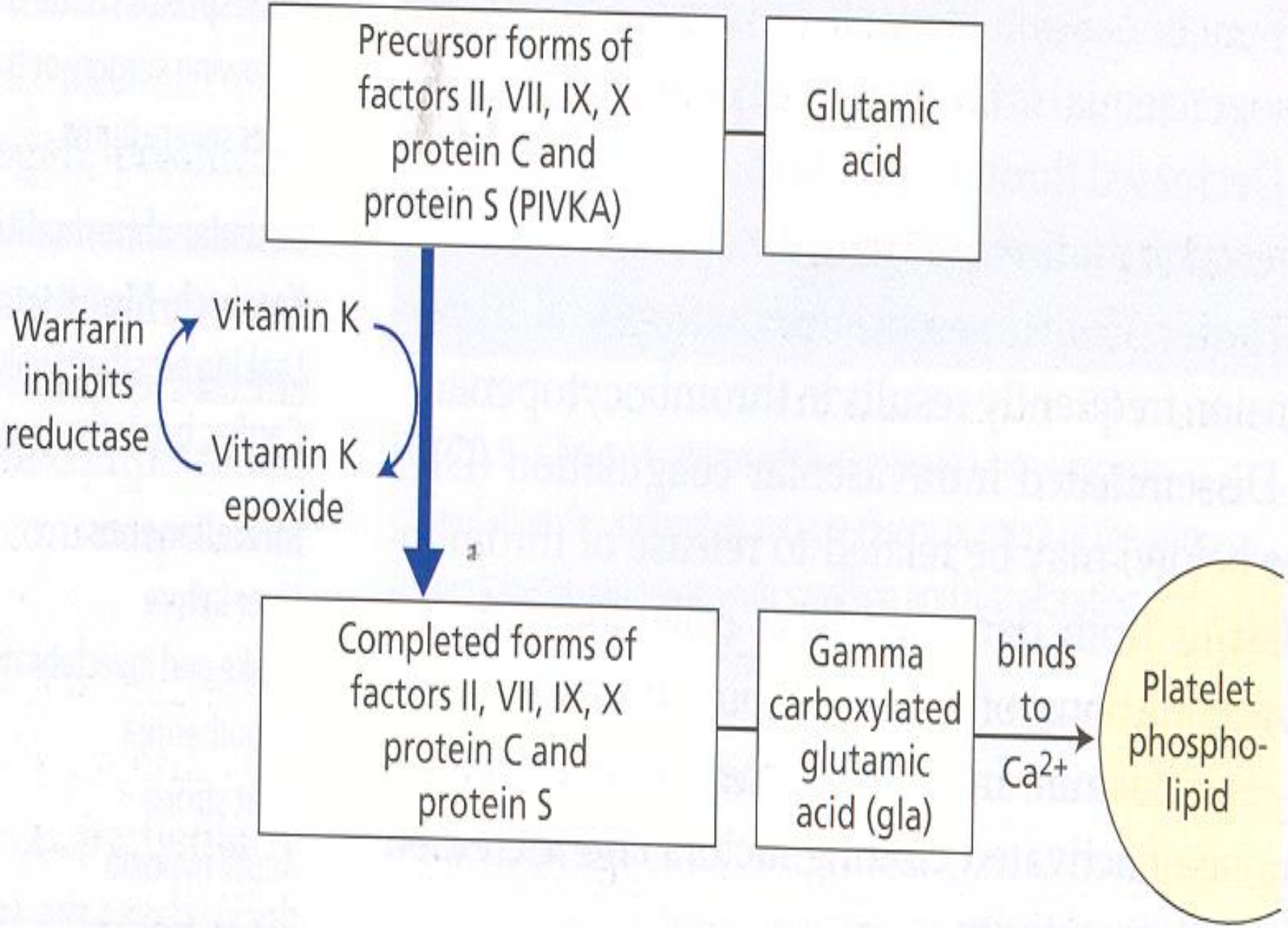
Antithrombotic Therapy

2- Oral anticoagulants

*** Antiplatelet drugs**

*** Warfarin**

*** New oral anticoagulant (Ximelagatran)**


Precursor forms of factors II, VII, IX, X protein C and protein S (PIVKA)
Glutamic acid
Warfarin inhibits reductase
Vitamin K
Vitamin K epoxide
Completed forms of factors II, VII, IX, X protein C and protein S
Gamma carboxylated glutamic acid (gla)
binds to Ca^{2+}
Platelet phospho-lipid

Oral Anticoagulants (Warfarin)

Doses and Preparations Available

- ✓ **Warfarin Preparations**

  Tablets 1 mg (Pink), 2 mg (Gray-Blue) 5 mg (Orange). 7.5 mg (Yellow) 10 mg (white)

- ✓ **Dosage: Large loading doses are no longer recommended. Depending on clinical circumstances, start with a daily dose of about 5 mg for 3 days. Check LFTs before starting treatment and do INR daily (the APTT as well) if the patient is receiving heparin, aiming to get the INR in the range between 2.0-4.5.**

- ✓ **The usual daily dose for most patients lies between 3 mg and 6 mg but maintenance doses may vary widely and regular control, by means of an INR performed at no longer than 8 weekly intervals, is mandatory.**

WARFARIN TAB. 1 mg

WARFARIN TAB. 2 mg

WARFARIN TAB. 2.5 mg

WARFARIN TAB. 5 mg

WARFARIN TAB. 7.5 mg

WARFARIN TAB. 10 mg

A lower dose of Warfarin may be required in any of the following:

a. Elderly
b. Poor nutrition
c. Liver disease
d. Potentiating drugs (especially antibiotics)
e. Heart failure
f. Following surgery

Oral Anticoagulants (Warfarin)

INR : International Normalized Ratio

ISI : International Sensitivity Index for the thromboplastin reagent used.

$$INR = \left(\frac{\text{Patient's PT}}{\text{Mean normal PT}} \right)^{ISI}$$

Oral anticoagulant control tests. Target INR levels.

Target INR	Clinical State
2.5 (2.0 – 3.0)	Treatment of DVT, pulmonary embolism, atrial fibrillation, recurrent DVT of warfarin; symptomatic inherited thrombophilia, cardiomyopathy, mural thrombus, cardioversion
3.5 (3.0 – 4.0)	Recurrent DVT while on warfarin, mechanical prosthetic heart valves, antiphospholipid syndrome (some cases)

Recommendations on the management of bleeding and excessive anticoagulation.

INR 3.0 – 6.0 (target INR 2.5)	**Reduce warfarin dose or stop**
INR 4.0 – 6.0 (target INR 3.5)	**Stop Warfarin,** **Restart warfarin when INR < 5.0**
INR 6.0 – 8.0 **No bleeding or minor bleeding**	**Stop warfarin,** **Restart when INR <5.0**
INR>8.0 **No bleeding or minor bleeding**	**Stop warfarin** **Restart warfarin when INR<5.0** **If other risk factors for bleeding** **give 0.5 – 2.5 mg of vitamin K orally**
Major bleeding	**Stop warfarin - Give prothrombin complex concentrate 50 units/kg or FFP 15 ml/kg** **Give 5 mg vitamin K (oral or i.v.)**

Drugs and other factors which interfere with the control of anticoagulant therapy

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Potentiation of oral anticoagulants

Drugs which increased the effect of coumarins

Reduced coumarin binding to serum albumin

- **sulphonamides**

Inhibition of hepatic microsomal degradation of coumarin

- **cimetidine**
- **allopurinol**
- **Tricyclic antidepressants**
- **metronidazole**
- **Sulphonamides**

Alteration of hepatic receptor site for drug

- **thyroxine**
- **quinidine**

Decreased synthesis of vitamin K factors

- **high doses of salicylates**
- **some cephalosporins**

Liver disease

Decreased synthesis of vitamin K factors

Decreased absoorption of vitamin K

e.g. malabsorption, anitibiotic therapy, laxatives

Inhibition of oral anticoagulants

Drugs which depress the action of coumarins

Acceleration of hepatic microsomal degradation of coumarin

- **barbiturates**
- **rifampicin**

Enhanced synthesis of clotting factors

- **Oral contraceptives**

Hereditary resistance to oral anticoagulants

Pregnancy

Coumadin
(WARFARIN)
Your Diet and Vitamin K

Why do you need to Pay attention to your diet?

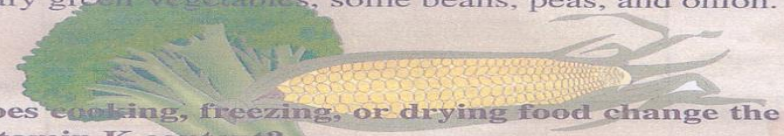
Because many kinds of food you eat have vitamin k in them, and Vitamin K helps your blood make clots.

Why should you stay on the same general diet every day?

Because major changes in the amount of Vitamin K you eat may affect the way your Coumadin (Warfarin) works. It is important for you to keep your diet steady. Don't make major changes in your diet before telling your healthcare provider, since your condition is affected.

Should you avoid foods with high amount of Vitamin K?

No. Just keep your diet steady. Some foods that are important to a healthy diet are high in Vitamin K, like leafy green vegetables, some beans, peas, and onion.



Does cooking, freezing, or drying food change the Vitamin K content?

There is little information about the effects of cooking, freezing, or drying on Vitamin K content in foods. It appears that the Vitamin K content of cooked, frozen, or dried food is about the same as fresh food.

How much Vitamin K does our food contain?

On the other side of the sheet you find a table listing the contents of Vitamin K for different kinds of food. The content estimation was made based on testing the same amount of each kind of food.

Remember that it is important to keep your diet steady!!

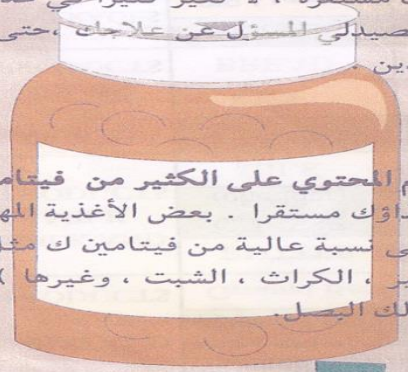
الكوميدين
(الوارفرين)
غذاؤك و فيتامين ك

لماذا عليك الإنتباه لغذائك؟

لأن الكثير من الطعام الذي تتناوله يحتوي على فيتامين ك و فيتامين ك يساعد على تخثر الدم.

لماذا يجب أن تبقى على غذاء متوازن كل يوم ؟

لأن التغيير في الكمية المأخوذة من فيتامين ك قد تؤثر على مفعول الكوميدين ، من المهم أن تحافظ على غذائك مستقرا حتى تكون كمية فيتامين ك مستقره ، لا تغير كثيرا في غذائك قبل أن تخبر الطبيب أو الصيدلي المسؤل عن علاجك ،حتى لا يؤثر على عمل الكوميدين.



هل يجب أن تتجنب الطعام المحتوي على الكثير من فيتامين ك ؟

لا.. فقط حافظ على غذاؤك مستقرا . بعض الأغذية المهمة للتغذية الصحية تحتوي على نسبة عالية من فيتامين ك مثل الخضروات الورقية (الجرجير ، الكراث ، الشبت ، وغيرها) و بعض الحبوب البقول وكذلك البصل.

هل الطبخ ، التجميد ، أو التجفيف يغير من محتوى فيتامين ك في الغذاء ؟

هناك معلومات بسيطة عن تأثير الطبخ ، التجميد ،أو التجفيف على الطعام و لكن يبدو أن فيتامين ك لا يتغير بالطعام المجمد ، المطبوخ ، أو المجفف عن الطازج .

كم يحتوي الطعام من فيتامين ك ؟

في الجهة المقابلة من النشرة ستجد جدولا للأطعمة المختلفة التي تحتوي على فيتامين ك ، المحتوى من فيتامين ك قيس على نفس الكمية من كل نوع من الأطعمة .

FOOD		PORTION SIZE	RANK of VITAMIN K CONTENT
FRUITS	Apple	1 apple	LOW
	Banana	1 banana	LOW
	Orange	1 orange	LOW
	Pears (canned)	1 cup	LOW
	Strawberries	1/2 cup	LOW
FATS	Oil	1 tablespoon	LOW
	Mayonnaise	7 tablespoon	MEDIUM
EGGS	Egg	1 whole egg	LOW
MEAT AND MEAT PRODUCTS	Beef Liver	120 Gm	HIGH
	Chicken (breast)	100 Gm	LOW
	Chicken Liver	100 Gm	MEDIUM
	Ground Beef	120 Gm	LOW
MILK AND MILK PRODUCTS	BUTTER	1 tablespoon	LOW
	CHEESE (cheddar)	100 gm	MEDIUM
	MILK	1 cup	LOW
CEREAL AND GRAIN PRODUCTS	OATS	1/2 cup	MEDIUM
	RICE	1/2 cup	LOW
	BREAD	1 slice	LOW
BEVERAGES	COFFEE	1 cup	MEDIUM
	TEA(grean)	1 cup	HIGH
VEGETABLES	ASPARAGUS	1/2 cup	MEDIUM
	BROCCOLI	1/2 cup	HIGH
	CABBAGE	1/2 cup	MEDIUM
	CHICK PEAS	1/2 cup	HIGH
	CORN	1/2 cup	LOW
	GREEN BEANS	1/2 cup	LOW
	KALE	1/2 cup	HIGH
	LETTUCE	1/2 cup	MEDIUM
	MOLOKIA	1/2 cup	MEDIUM
	POTATO	1/2 cup	LOW
	PUMPKIN	1/2 cup	LOW
	PARSLEY	1/2 cup	MEDIUM
	SPINACH	1/2 cup	MEDIUM
	TOMATO	1 medium	LOW

الغذاء		الكمية	محتوى فيتامين ك
فاكهة	تفاح	حبة تفاح	منخفض
	موز	حبة موز	منخفض
	برتقال	حبة برتقال	منخفض
	أجاص	حبة أجاص	منخفض
	فراولة	٢/١ كوب	منخفض
لدهون	زيت	١ ملعقة طعام	منخفض
	مايونييز	٧ ملاعق طعام	متوسط
البيض	بيض	١ بيضة	منخفض
الحوم و منتجات الحوم	كبدة البقر	١٢٠ جرام	عالي
	دجاج	١٠٠ جرام	منخفض
	كبدة الدجاج	١٠٠ جرام	متوسط
	لحم مفروم	١٢٠ جرام	منخفض
الحليب منتجات الحليب	جبنة تشيدر	١٠٠جرام	متوسط
	زبدة	١ ملعقة طعام	منخفض
	حليب	١ كوب	منخفض
حبوب و مشتقاتها	خبز أبيض	١ شريحة	منخفض
	رز	٢/١ كوب	منخفض
	قمح	٢/١كوب	متوسط
مشروبات	القهوة	١ كوب	متوسط
	الشاي الأخضر	١ كوب	عالي
خضروات	هليون	٢/١ كوب	متوسط
	قرنبيط أخضر	٢/١ كوب	عالي
	ملفوف	٢/١ كوب	متوسط
	حمص	٢/١ كوب	عالي
	ذرة	٢/١ كوب	منخفض
	فاصوليا	٢/١ كوب	منخفض
	كيل	٢/١ كوب	عالي
	خس	٢/١ كوب	متوسط
	بطاطس	٢/١ كوب	منخفض
	قرع	٢/١ كوب	منخفض
	سبانخ	٢/١ كوب	متوسط
	طماطم	حبة متوسطة	منخفض
	ملوخية	٢/١ كوب	متوسط

Fibrinolytic agents – plasminogen activators

- **Streptokinase (SK)**
- **Tissue plasminogen activator (tPA)**
- **Single – chain urokinase-type plasminogen activator (SCU – PA)**
- **Acylated plasminogen – streptokinase activator complex (APSAC)**

Contraindications to thrombolytic therapy

Absolute contraindications	Relative contraindications
Active gastrointestinal bleeding	Traumatic cardiopulmonary resuscitation
Aortic dissection	Major surgery in the past 10 days
Head injury or cerebrovascular accident in the past 2 months	Past history of gastrointestinal bleeding
Neurosurgery in the past 2 months	Recent obstetric delivery
Intracranial aneurysm or neoplasm	Prior arterial puncture
Proliferative diabetic retinopathy	Prior organ biopsy
	Serious trauma
	Severe arterial hypertension (systolic pressure >200 mmHg, diastolic pressure >110 mmHg)
	Bleeding diathesis


Thank you!
TESCHIO 99