Blood coagulation disorders

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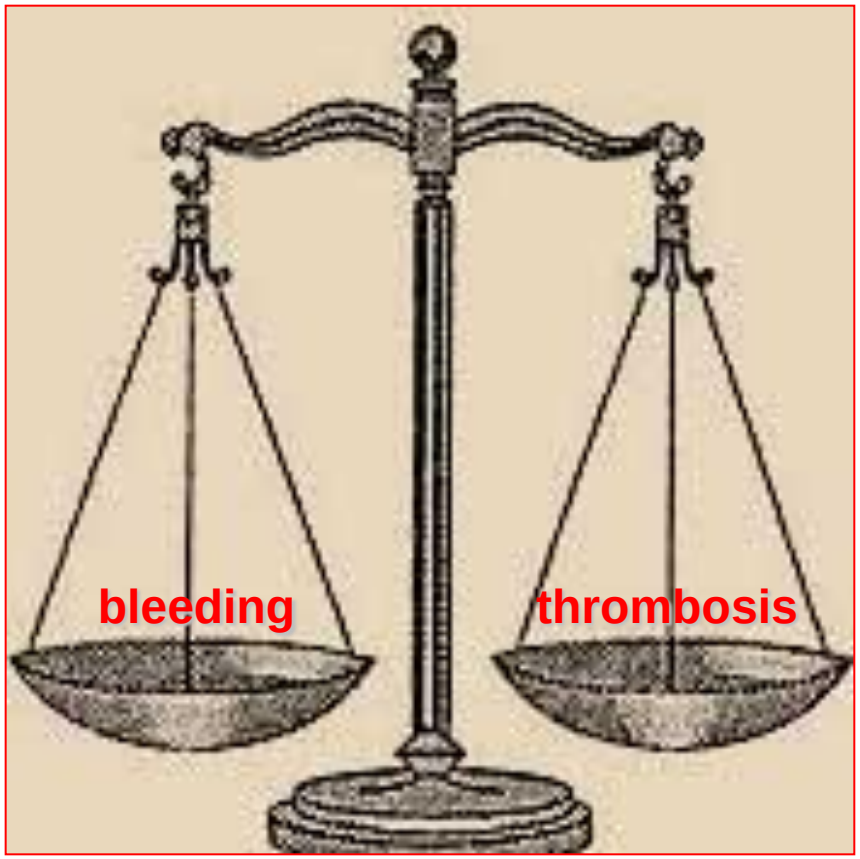
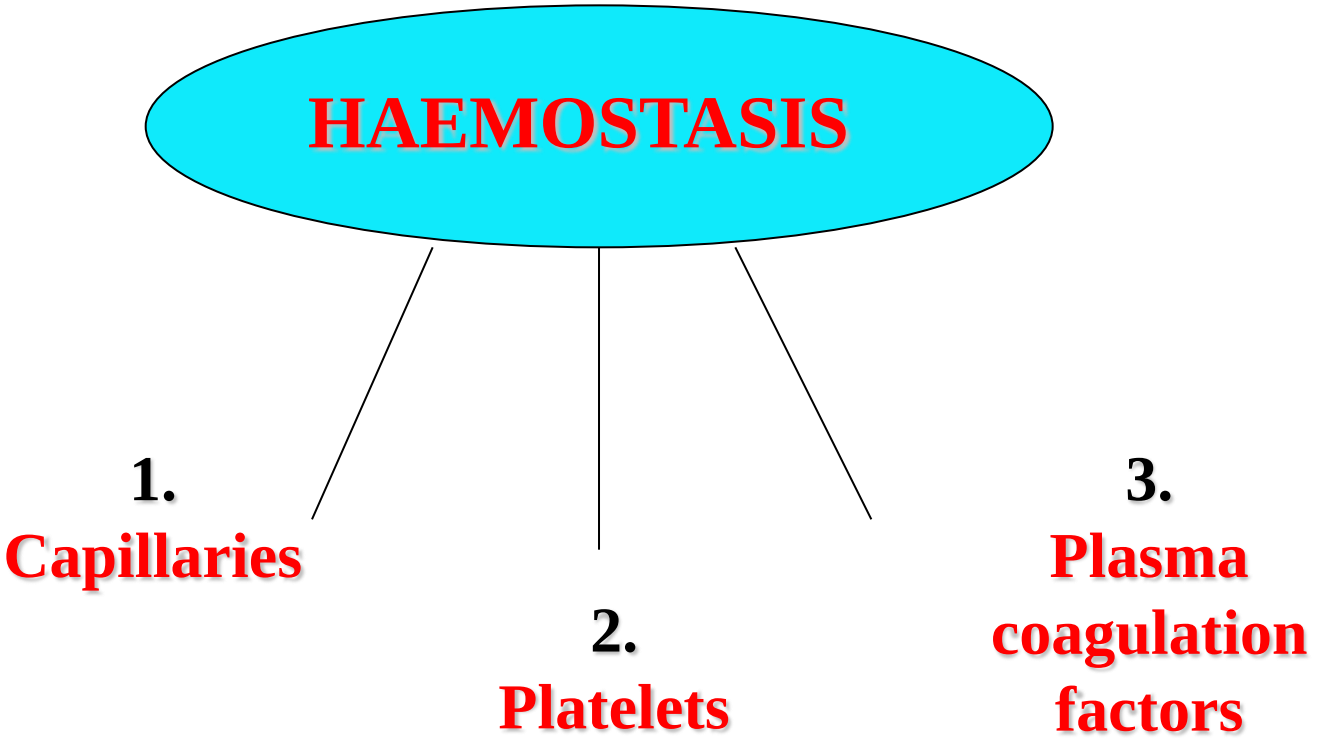
The normal haemostasis prevents:

- spontaneous haemorrhage and undue blood loss from injured vessels
- intravascular thrombus formation.



There are three components of blood coagulation system:

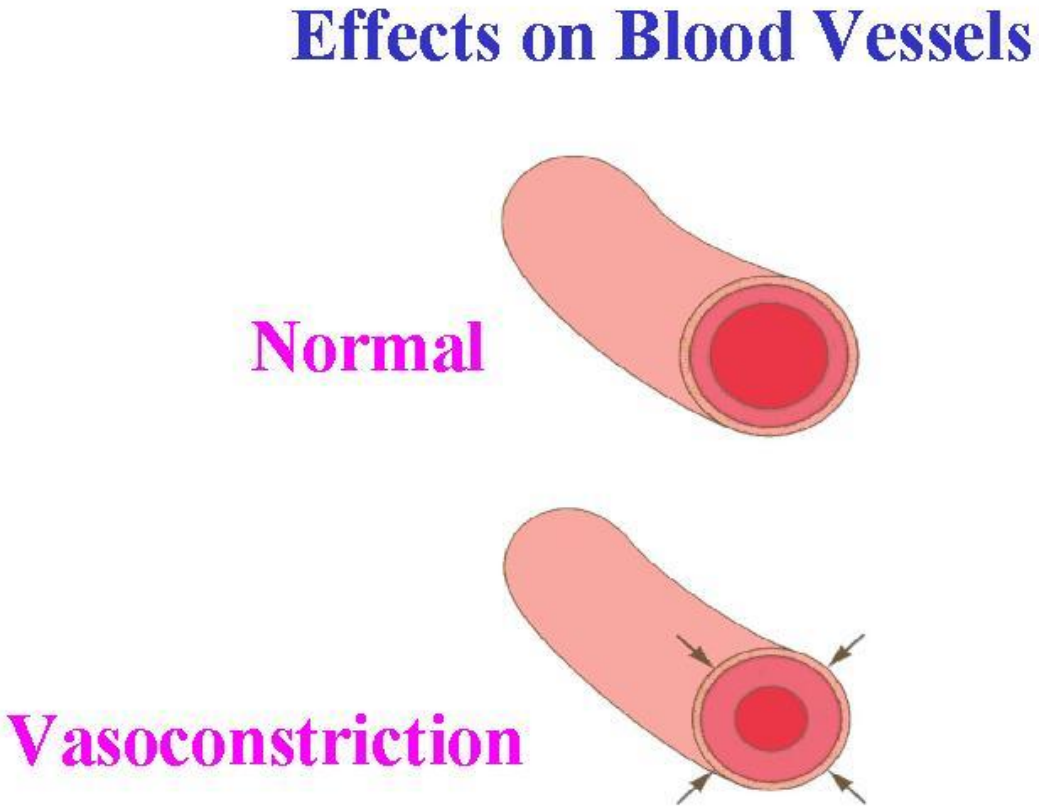


1. 2: Primary haemostasis (it is enough to stop bleeding from small injuries)

3: Secundary haemostasis (it is necessary to stop bleeding definitely)

Primary haemostasis I:

- **Capillaries and larger blood vessels react to injury by an immediate local temporary *vasoconstriction* (a reflex nervous mechanism) to reduce the amount of blood lost.**



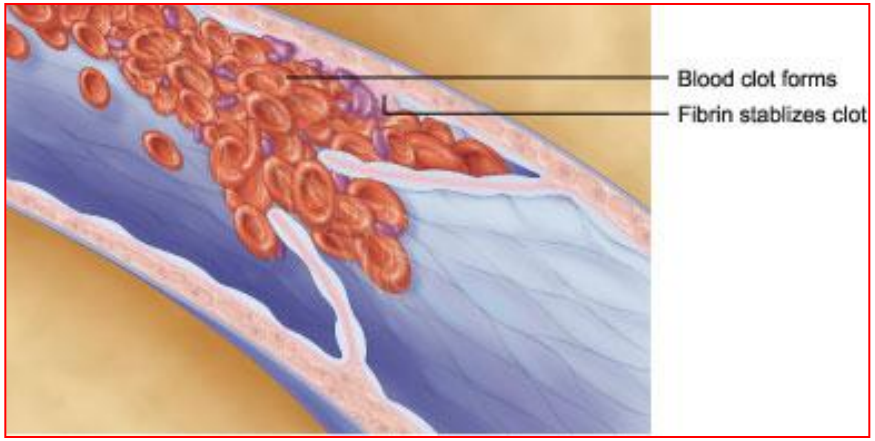
Primary haemostasis II:

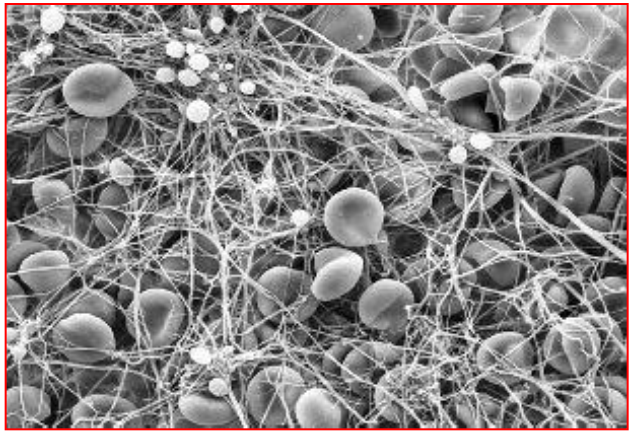
- **Platelets:**

- *adhere* to the site of injury

- *aggregation*

- *release* substances from their cytoplasms to initiate blood coagulation ⇒ *haemostatic platelet plug is formed.*

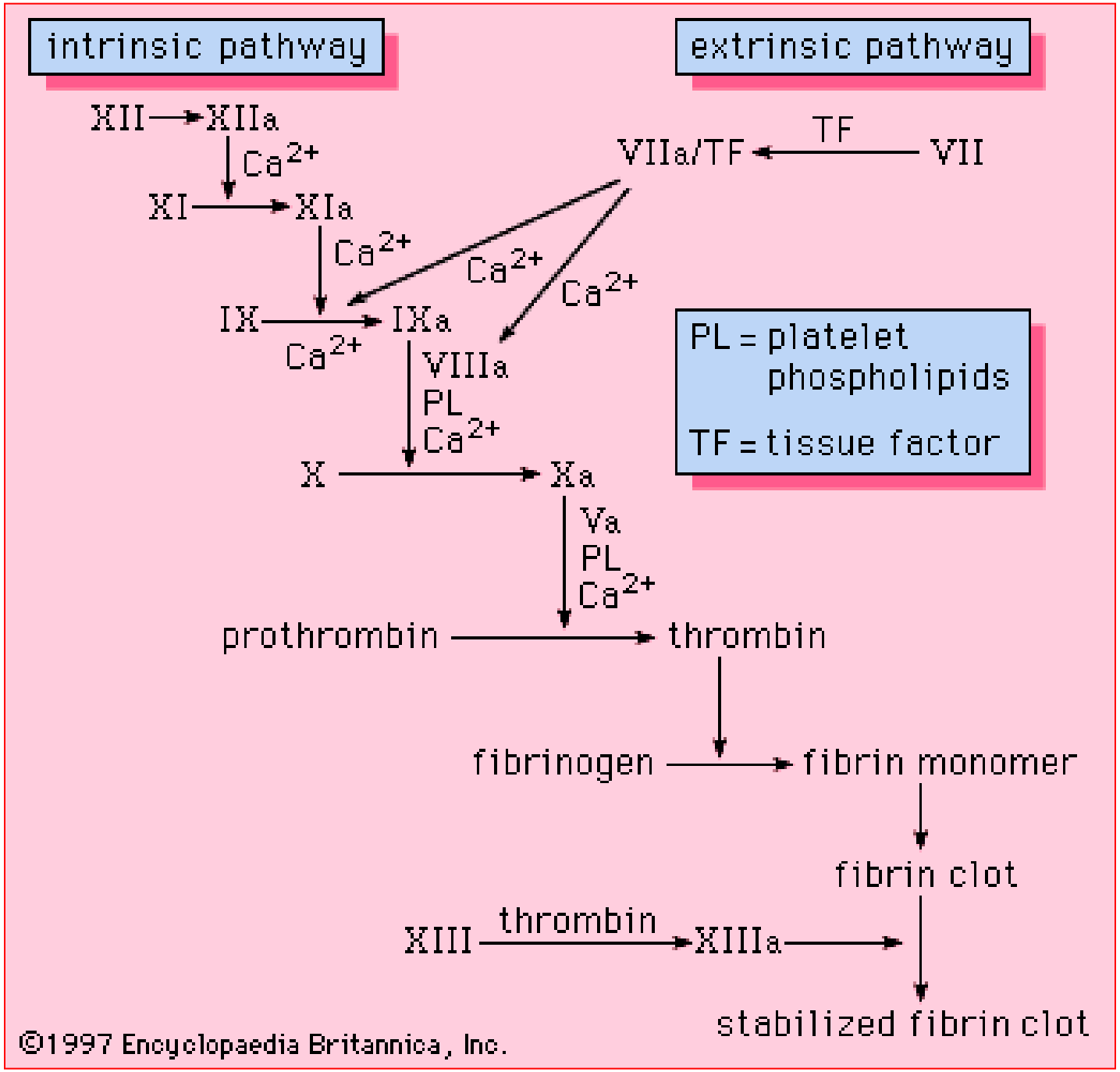




Secundary haemostasis:

Blood coagulation factors are necessary to stop bleeding definitely.

- I: fibrinogen
- II: prothrombin
- III: tissue thromboplastin (tissue factor, TF)
- IV: Ca^{++}
- V: proaccelerin
- VI: - (= FVa)
- VII: proconvertin
- VIII: antihemophilic factor (AHF)
- IX: Christmas factor (plasma thromboplastin component)
- X: Stuart factor
- XI: plasma thromboplastin antecedent (PTA)
- XII: Hageman factor (contact factor)
- XIII: fibrin stabilizing factor (Laki-Lorand factor)


intrinsic pathway
extrinsic pathway
XII → XIIa
Ca2+
XI → XIa
Ca2+
IX → IXa
Ca2+
VIIIa
PL
Ca2+
X → Xa
Va
PL
Ca2+
prothrombin → thrombin
fibrinogen → fibrin monomer
fibrin clot
XIII thrombin → XIIIa
stabilized fibrin clot
VIIa/TF ← TF — VII
Ca2+
Ca2+
PL = platelet phospholipids
TF = tissue factor
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Disorders of the haemostatic mechanism are devided into three main groups:

- **Disorders of the vessels**
- **Disorders of the platelets**

} ***„ purpuric diseases”***

- **Disorders of the blood coagulation mechanism *(„coagulopathies”)***

The investigation of a patient with a suspected disorder of haemostasis

- case history (personal details, family history)
- inspection (type of bleeding)
- physical examination
- other known diseases
- drugs and medications
- laboratory tests

Certain signs and symptoms are virtually diagnostic of disordered haemostasis.

The main symptom of all diseases is the bleeding:

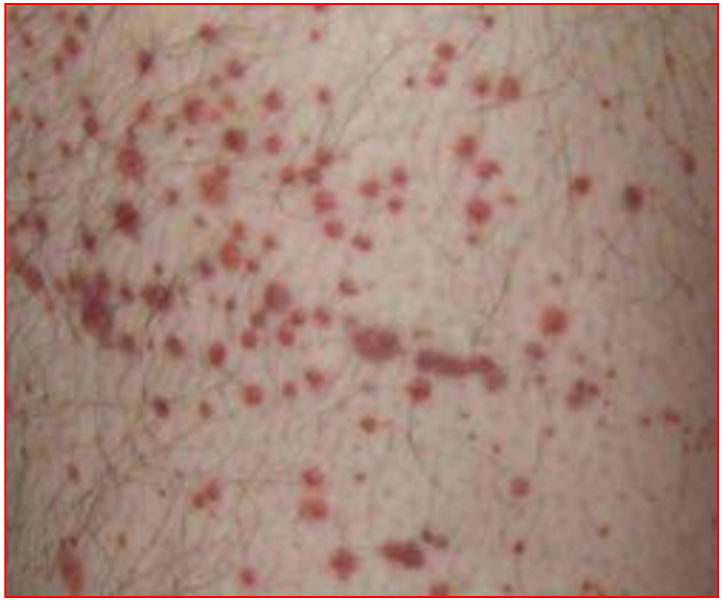
- **in the „purpuric disorders" cutaneous and mucosal bleeding usually is prominent**
- **in different types of „coagulopathies" hemarthroses, haematomas are the characteristic bleeding manifestations.**

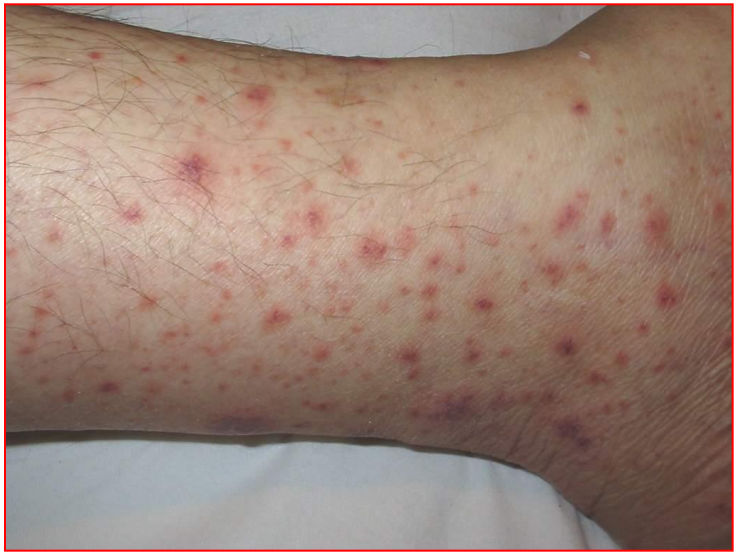
The onset of bleeding following trauma frequently is *delayed* (recur in a matter of hours)

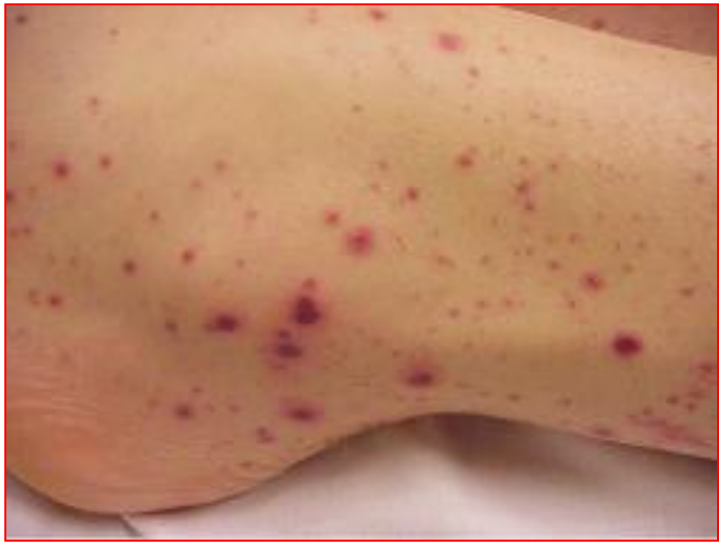
(the temporary hemostatic adequacy of the platelet plug may explain this phenomenon).

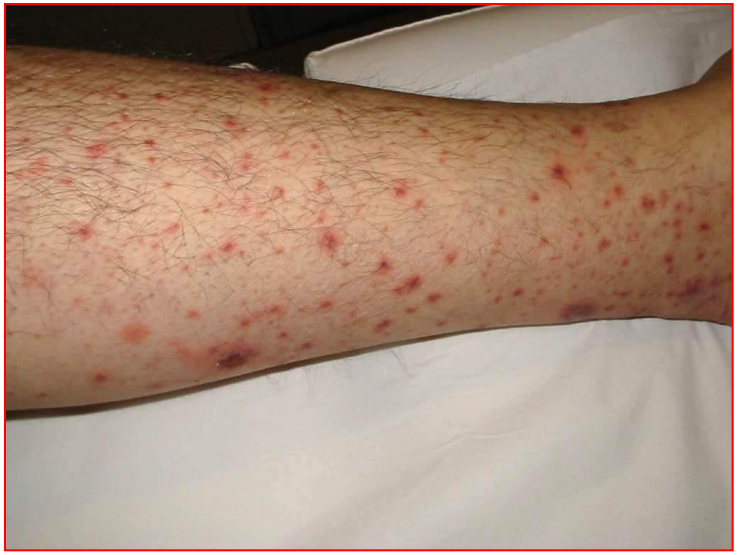
Petechiae, purpuras:

small capillary haemorrhages ranging from the size of a pinhead to much larger



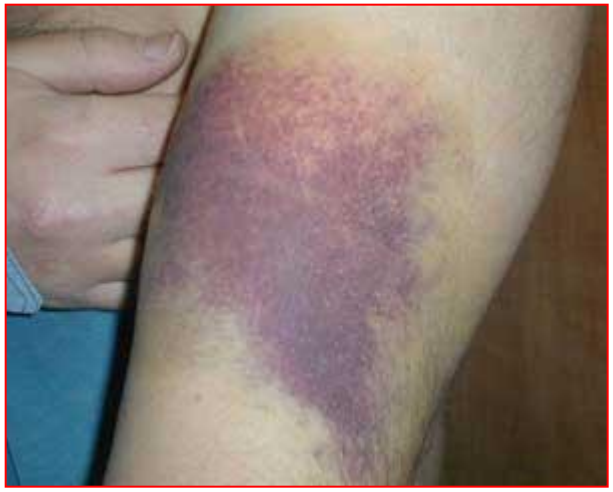


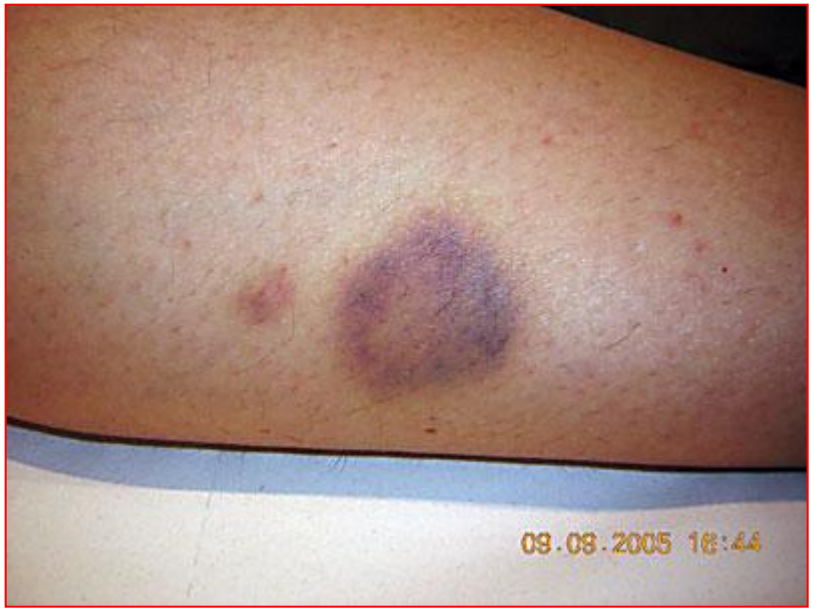


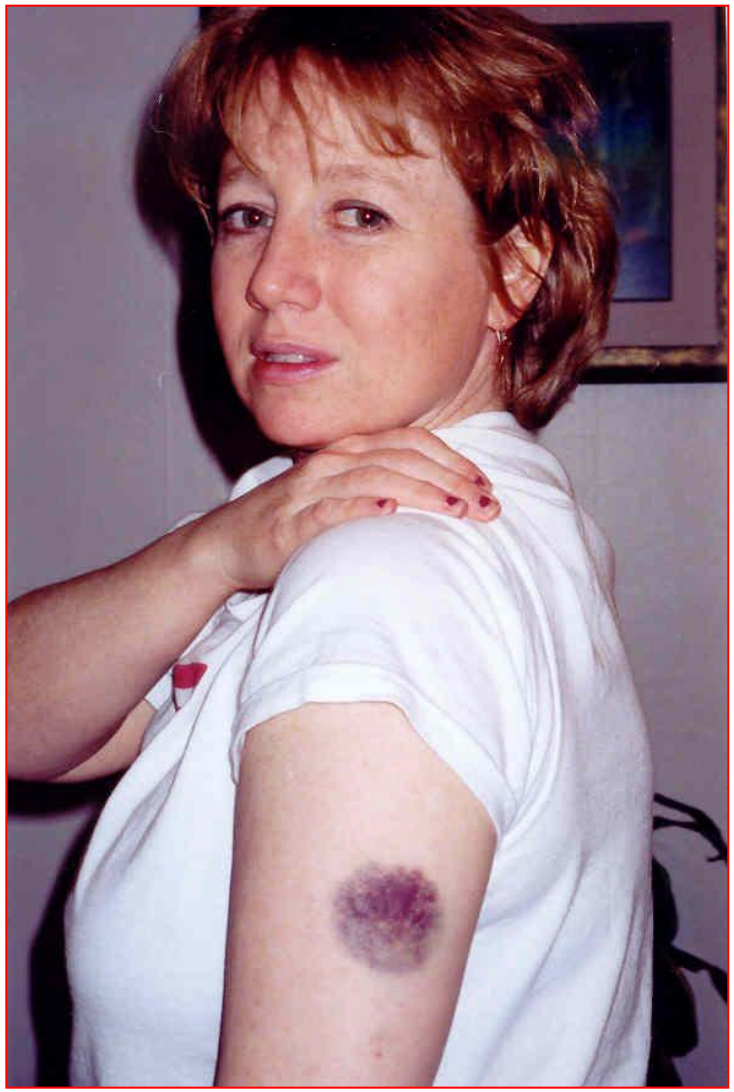


Haematomas:

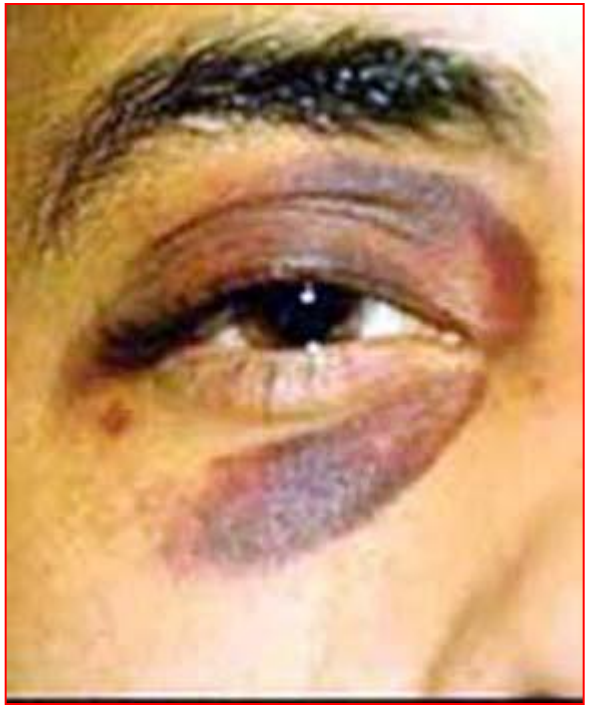
may be spontaneous (in a serious hemorrhagic disease) or may occur after trauma (in a mild hemorrhagic disease).

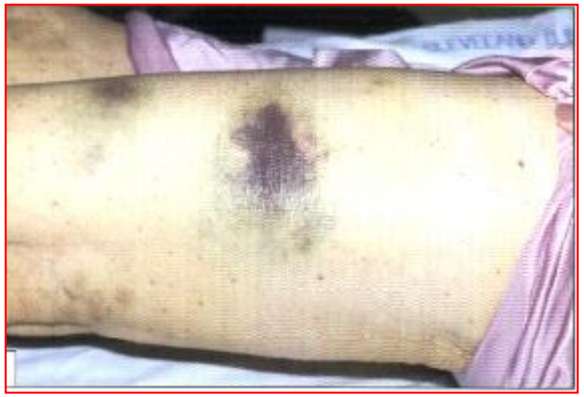


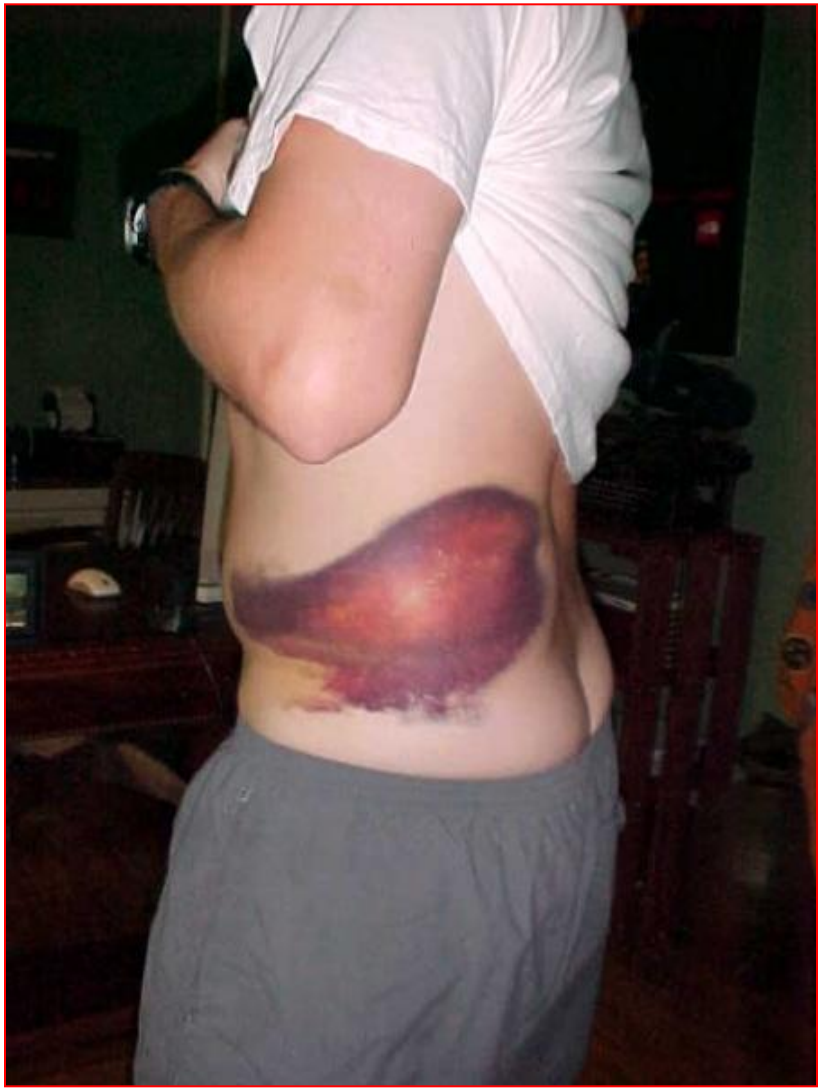




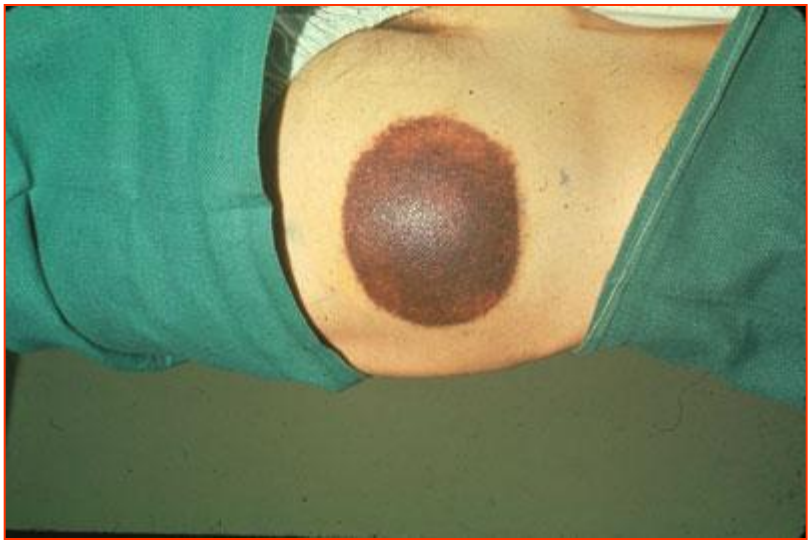
Haematomas

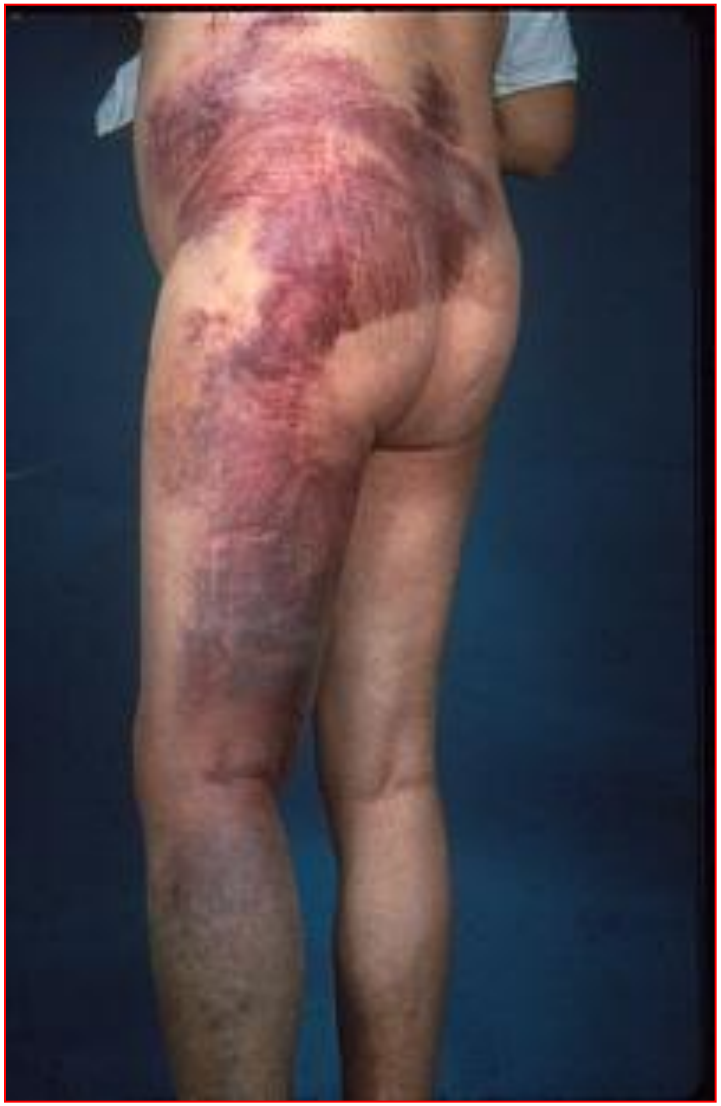






Intramuscular injection may be very dangerous to the patient with a bleeding disorder!

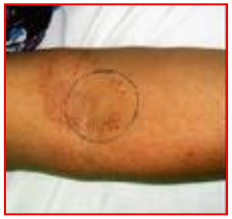


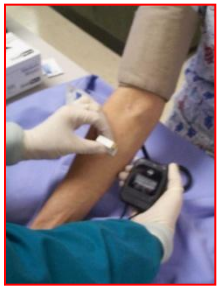


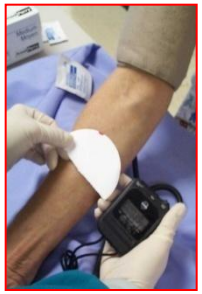
Venipuncture (if skilfully performed) is without danger becouse the elasticity of the venous walls.

Screening tests of blood coagulation

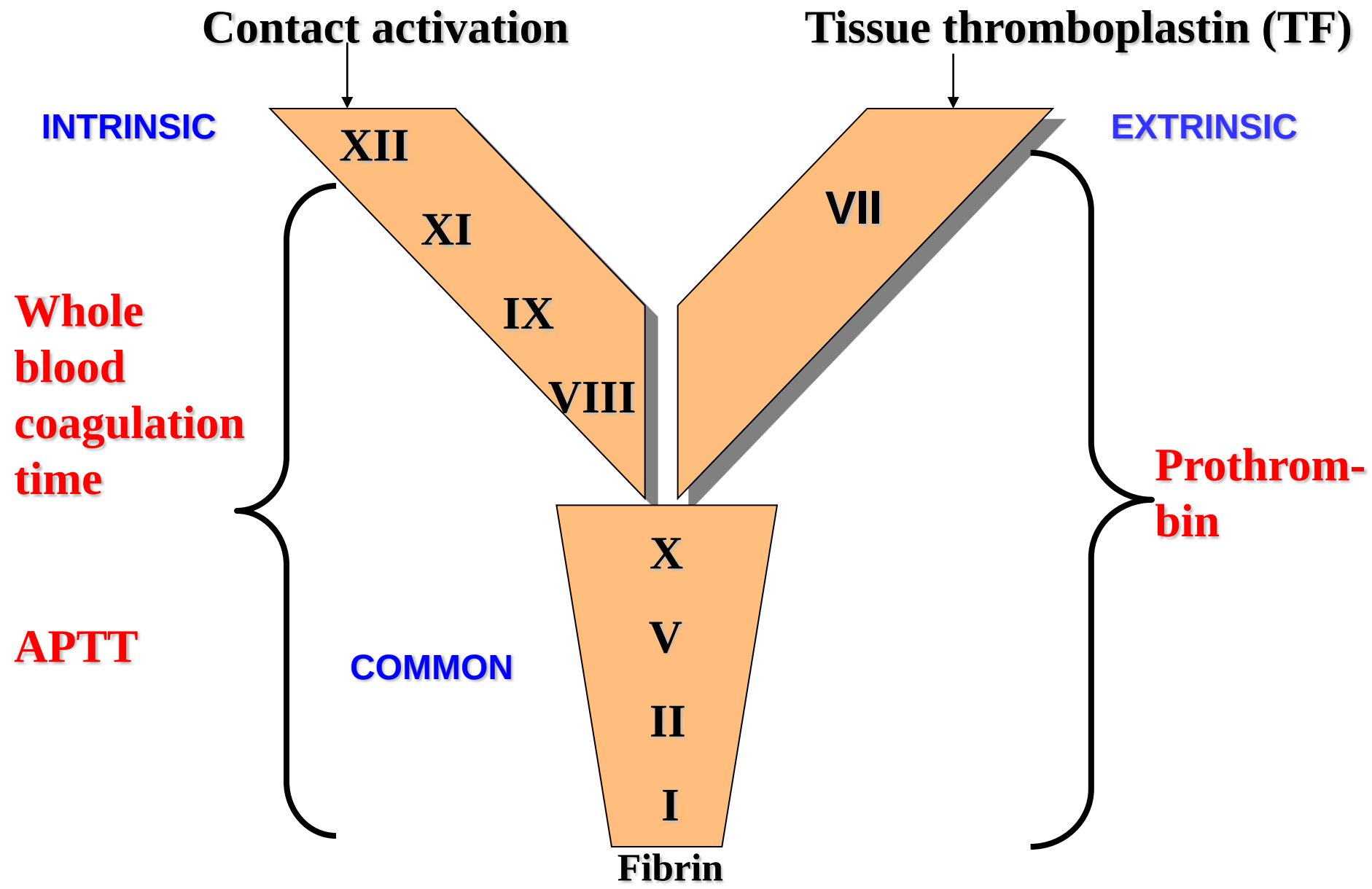
- **Disorders of vessels:**
  - Rumpel-Leede test
- **Disorders of platelets:**
  - Platelet count and morphology
  - Bleeding time (Ivy)
- **Coagulopathies:**
  - Whole blood coagulation time
  - Aktivated partial thromboplastin time (APTT)
  - Prothrombin (INR)
  - Thrombin time (TT)







Laboratory diagnosis of the coagulopathies



Diagnosis of bleeding disorders by the screening tests

Platelet count	Bleeding time	APTT	Prothrom-bin	Presumptive diagnosis
Decreased	Prolonged	Norm.	Norm.	*Thrombocytopenia*
Norm.	Prolonged	Prolonged	Norm.	*von Willebrand's disease*
Norm./ increased	Prolonged	Norm.	Norm.	*Thrombocytopathia*
Norm.	Norm.	Prolonged	Norm.	*„intrinsic" pathway abnormality* (FVIII. IX. XI. XII)
Norm.	Norm.	Norm.	Prolonged	*„extrinsic"pathway abnormality* (FVII)
Norm.	Norm.	Prolonged	Prolonged	*„common" pathway abnorm.* (FI. II. V. X.)
Norm.	Norm.	Norm.	Norm.	*- /FXIII deficiency/ mild bleeding disorder*

Coagulopathies

- **Aquired:**
  generally several coagulation abnormalities are present. Clinical picture is complicated by signs and symptoms of *the underlying disease*.

  - **Deficiencies of the vitamin K dependent coagulation factors (FII, VII, IX, X)**
  - **Hepatic disorders**
  - **Accelerated destruction of blood coagulation (DIC)**
  - **Inhibitors of coagulation**
  - **Others (massive transfusion, extracorporal circulation)**

- **Hereditary:**
  deficiency or abnormality of a single coagulation factor.

  - **Hemofilia A (FVIII)**
  - **Hemofilia B (FIX)**
  - **Von Willebrand's disease**
  - **Rare coagulopathies (FI. II. V. VII. X. XI. XIII)**

Haemophilia

A bleeding disorder in which clotting factor VIII (eight) *Haemophilia A/* or IX (nine) *Haemophilia B/* in a person's blood plasma is missing or is at a low level.

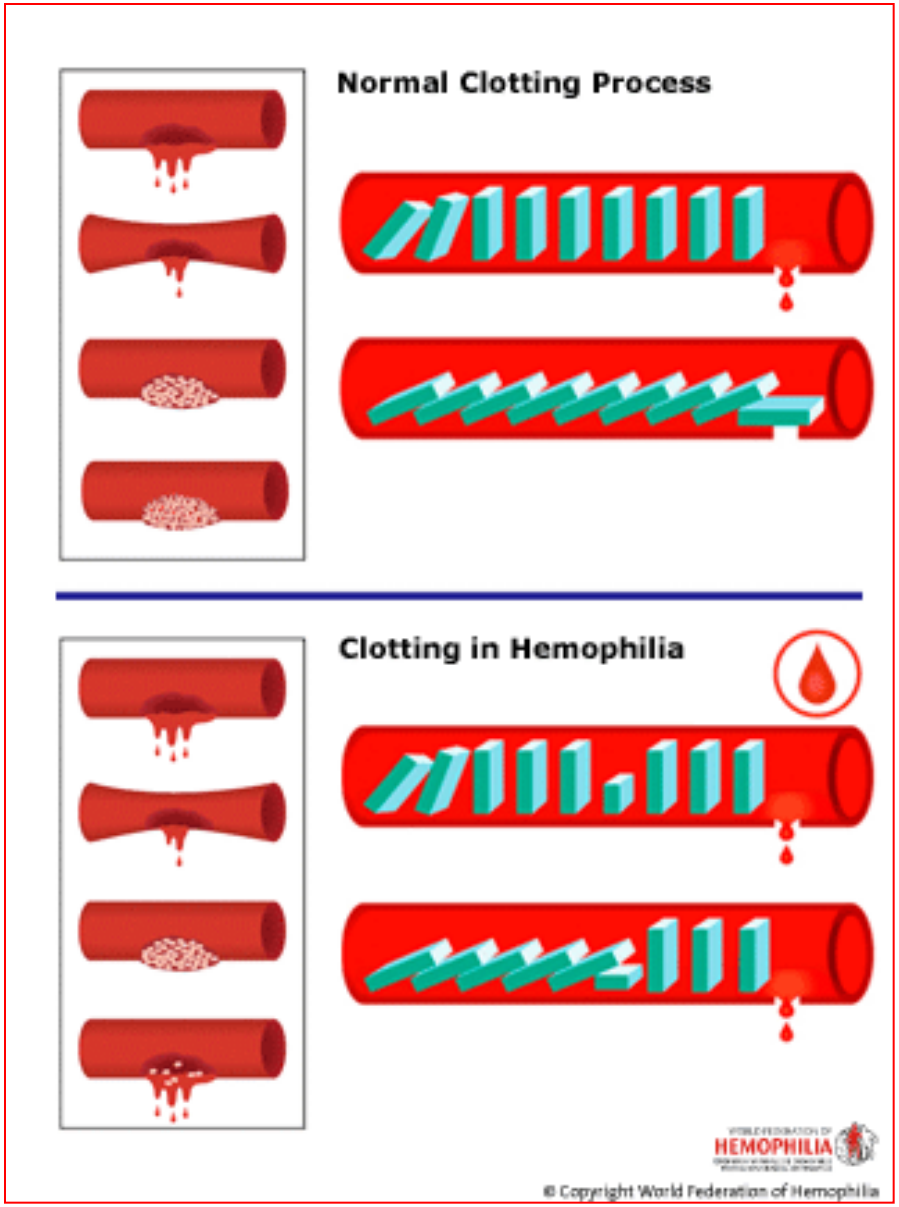
Prevalence:

haemophilia A: 105/million men

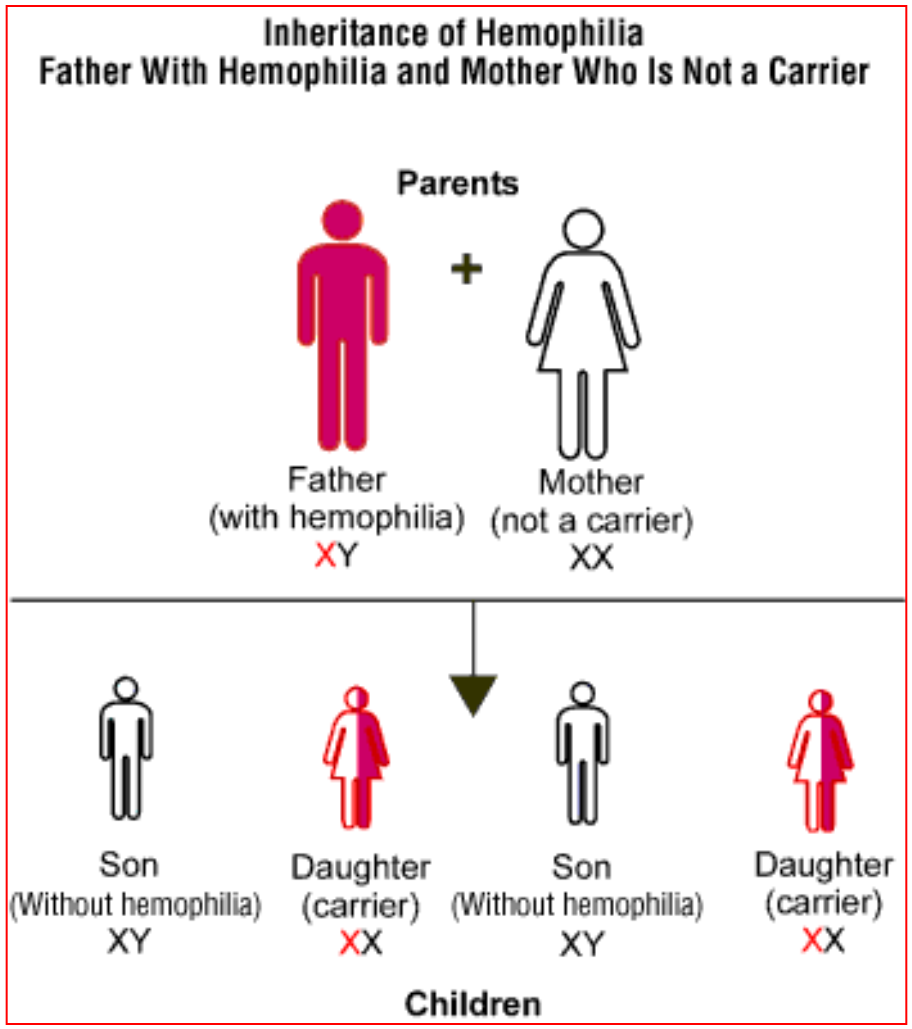
haemophilia B: 28/million men

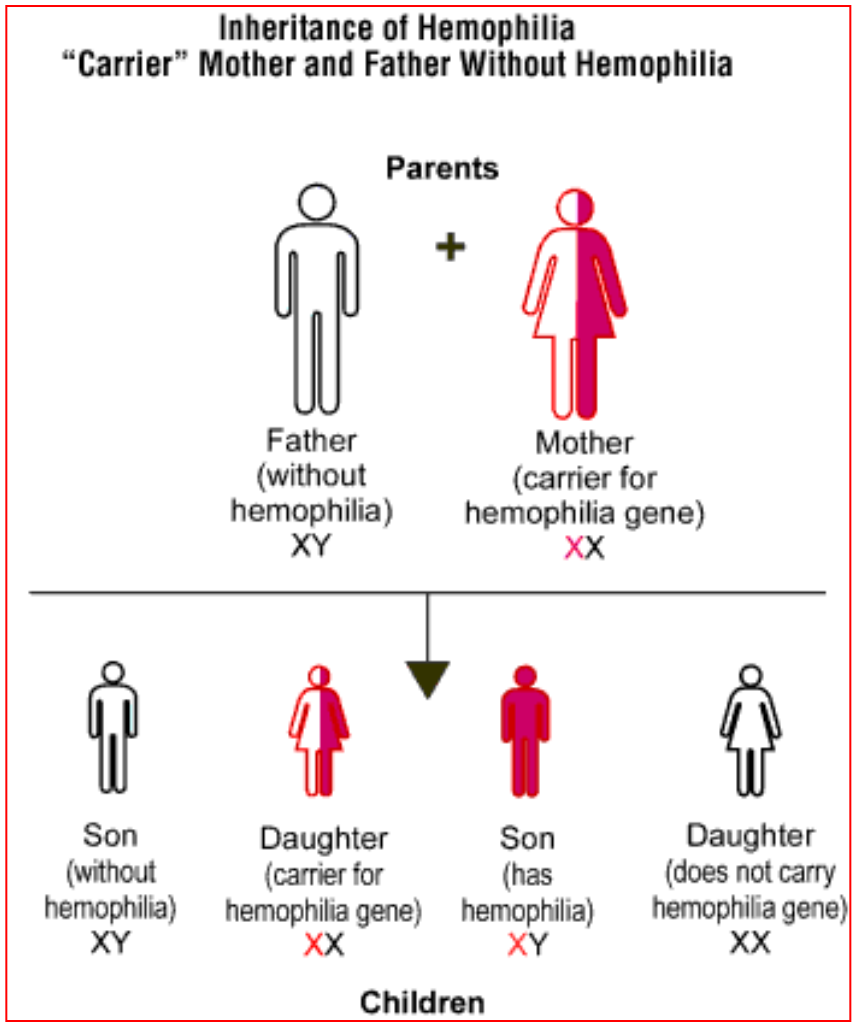
- **In haemophilia, VIII or IX clotting factor is missing, or the level of that factor is low.**

- **This makes it difficult for the blood to form a clot, so bleeding continues longer than usual.**



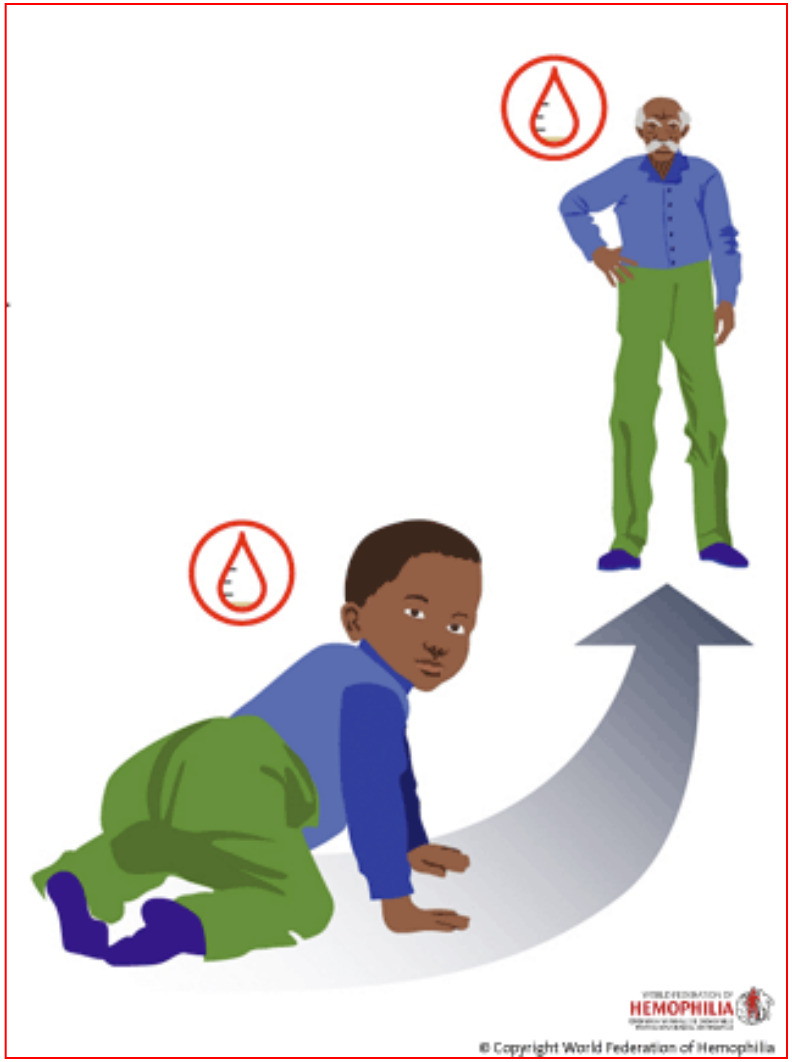
The hemophilia gene is carried on the X chromosome
⇒ in males who lack a normal allele, the defect is manifested by clinical haemophilia. Women may be carriers.





Haemophilia is a lifelong disease

- A person born with haemophilia will have it for life.
- The level of factor VIII or IX in his blood usually stays the same throughout his life.



Clinical manifestations

The most dramatic manifestation of haemophilia is extensive bleeding into the soft tissue and muscles *after only negligible trauma, or even no known trauma.*

The frequency and severity of bleeding generally is related to the blood level of FVIII or FIX.

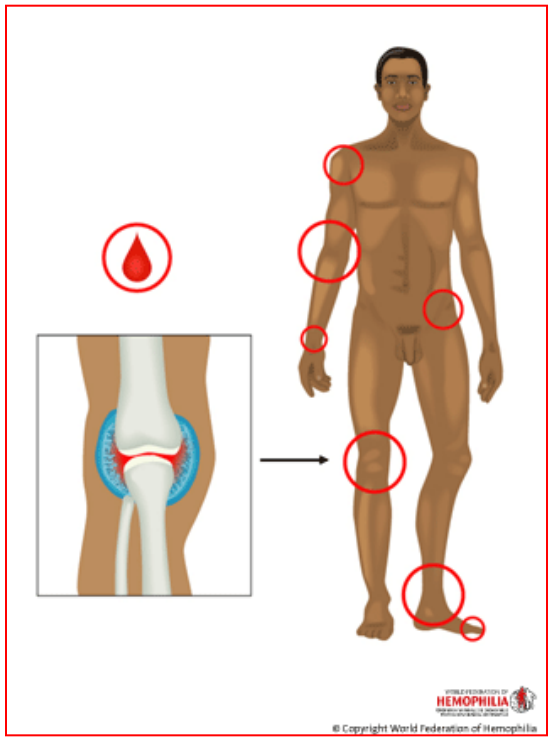
Haemophilia can be mild, moderate, or severe, depending on the level of clotting factor. Three category of severity:

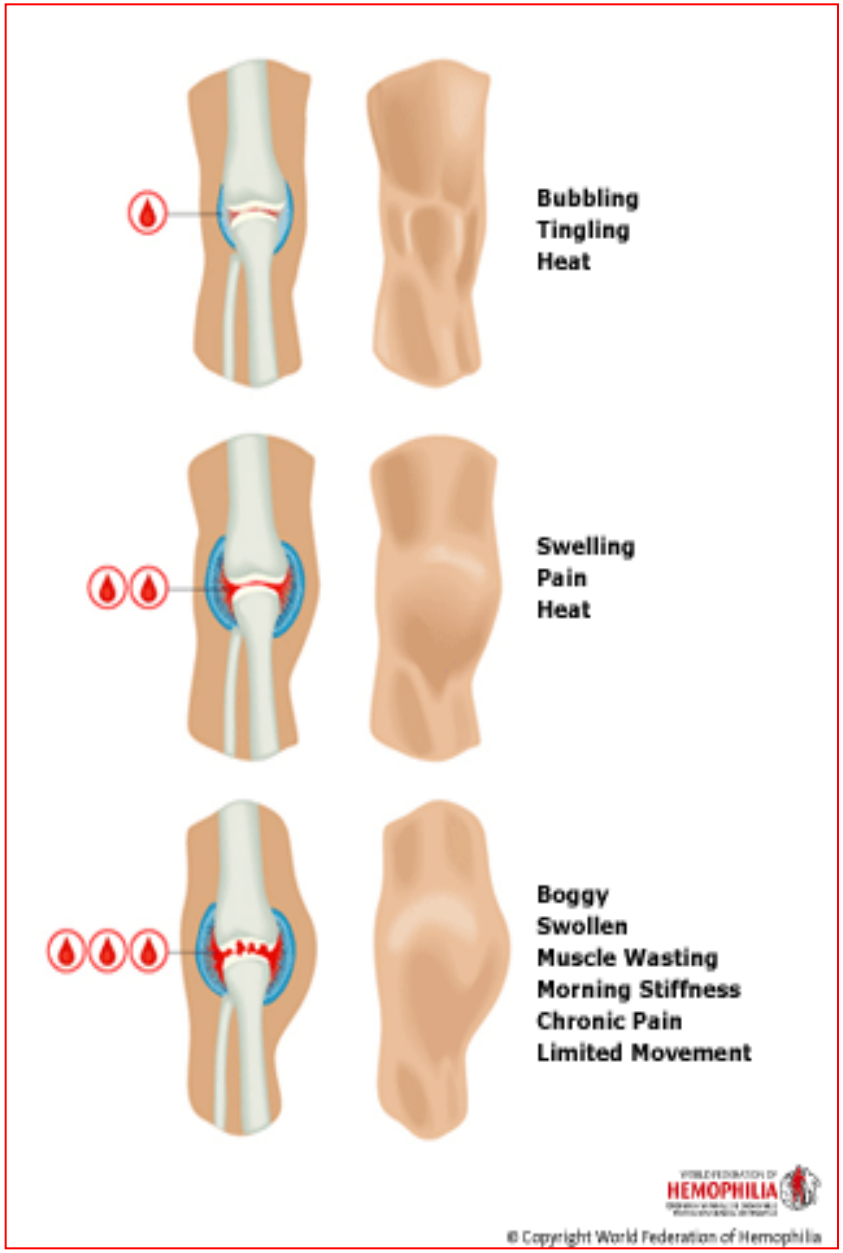
- **Severe: FVIII/FIX < 1 %**
  - **Repeated and severe hemarthroses and spontaneous bleeding, crippling common.**
- **Moderate: FVIII/FIX: 1-5 %**
  - **Spontaneous bleeding and hemarthroses infrequent. Serious bleeding from trivial injuries.**
- **Milde: FVIII/FIX: 5-40 %**
  - **Spontaneous bleeding manifestations may be absent, although serious bleeding may follow surgical procedures or traumatic injury.**

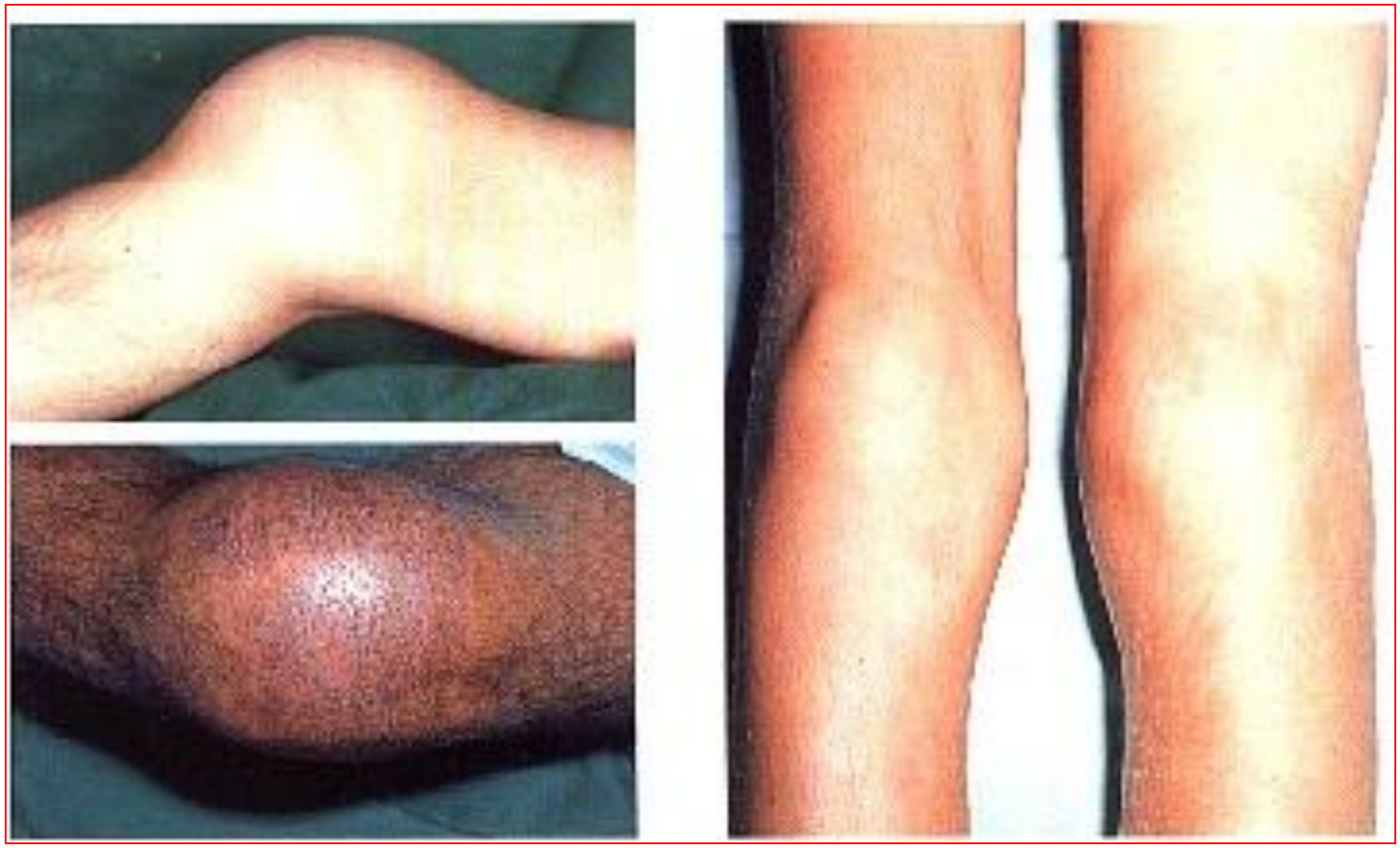
Joint bleeding

As blood fills the capsule, the joint swells and becomes painful and hard to move.

The most common joint bleeds happen in ankles, knees, and elbows.
Bleeds into other joints can also happen.



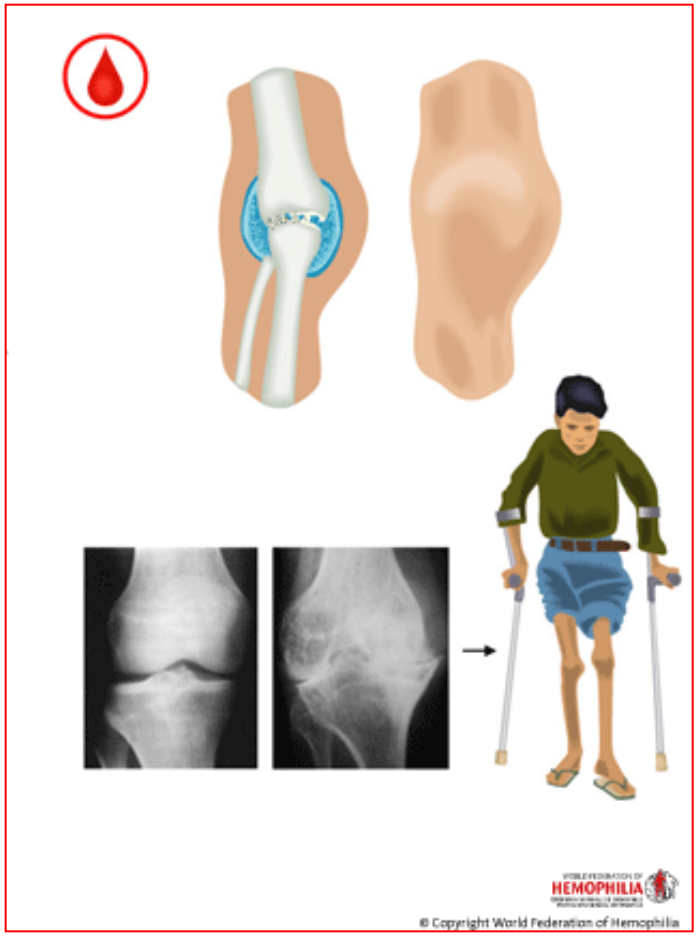




The long-term effects of joint bleeds:

Repeated bleeding into a joint causes the synovium to swell and bleed very easily. Some blood remains in the joint after each bleed. The synovium stops producing the slippery, oily fluid that helps the joint move. This damages the smooth cartilage that covers the ends of the bones. The joint becomes stiff, painful to move, and unstable. It becomes more unstable as muscles around the joint weaken.

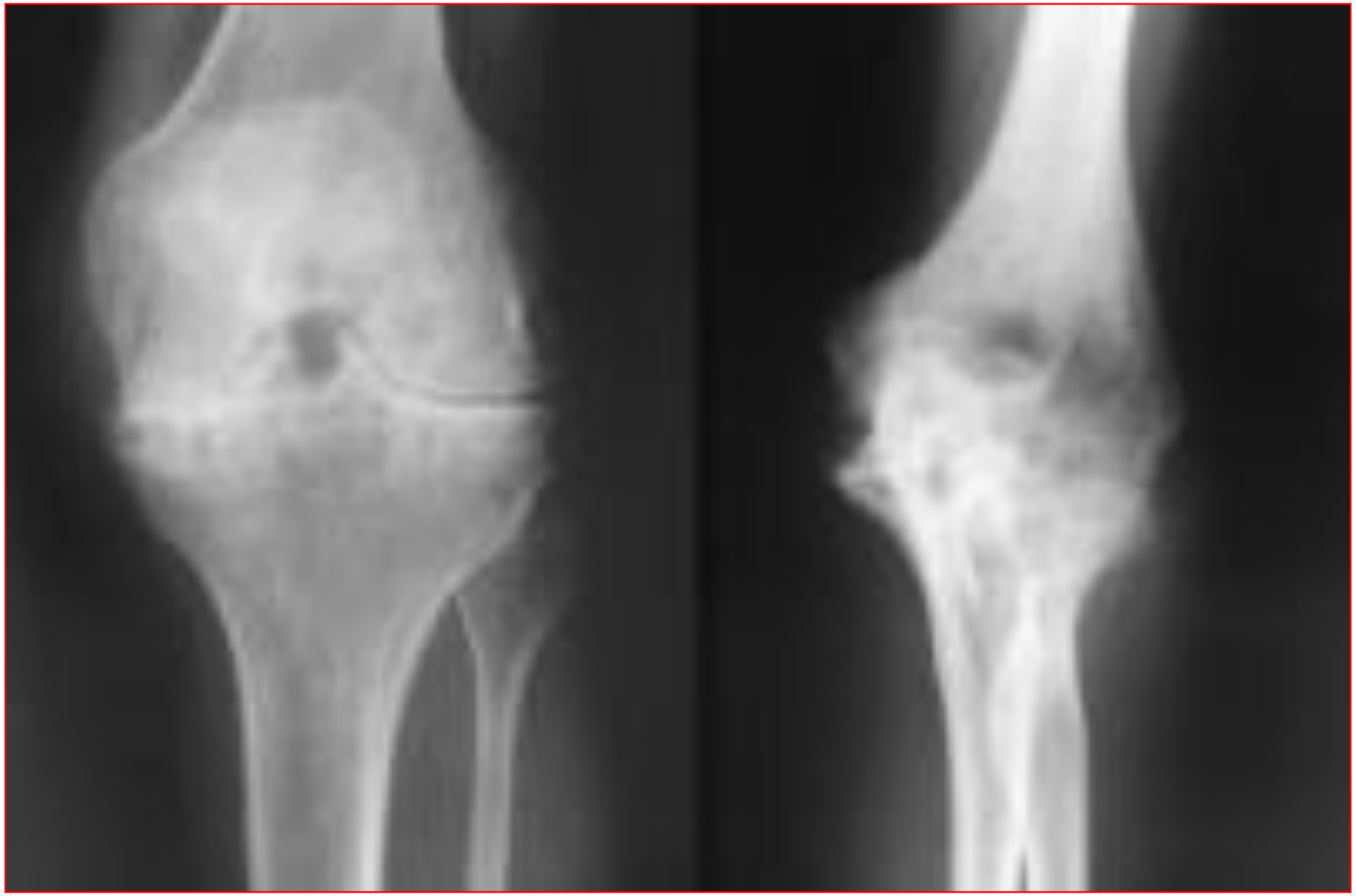
With time, most of the cartilage breaks down and some bone wears away. Sometimes the joint cannot move at all.

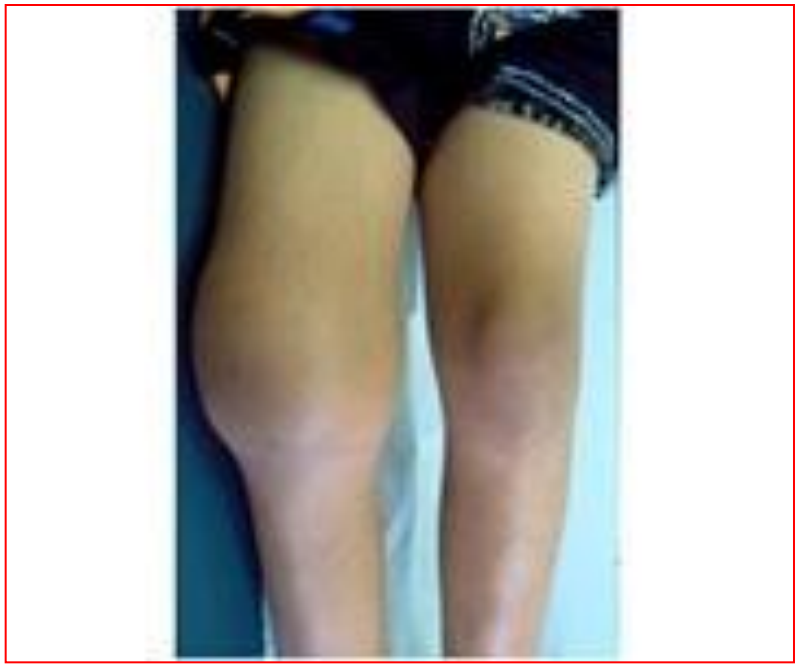


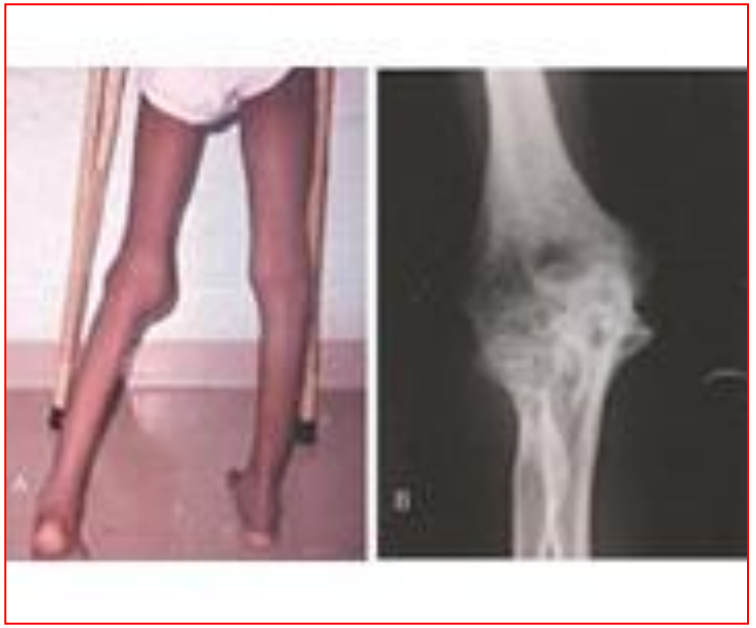
The whole process is called:

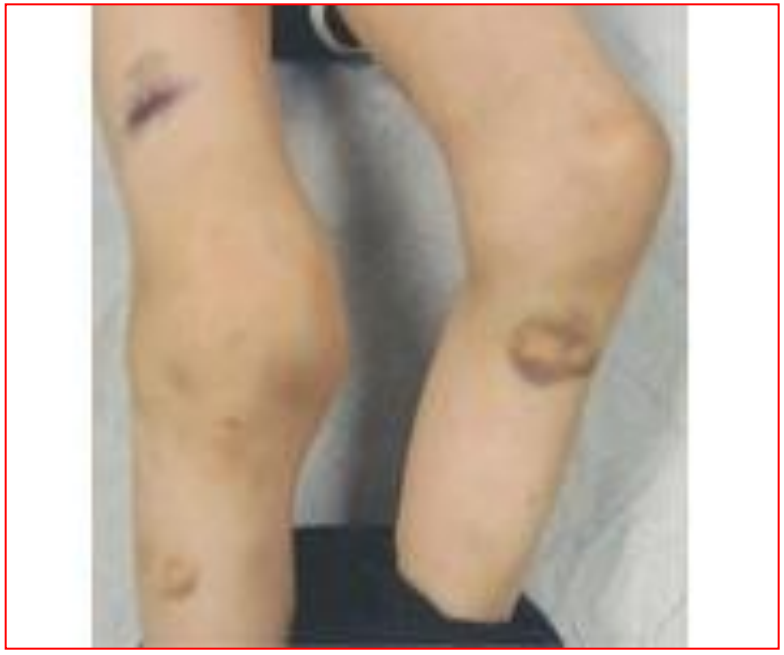
hemophilic arthritis.

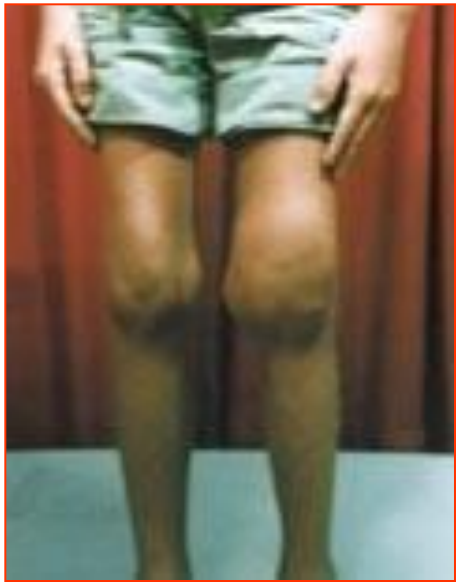
Haemophilic arthropathy (radiographs)

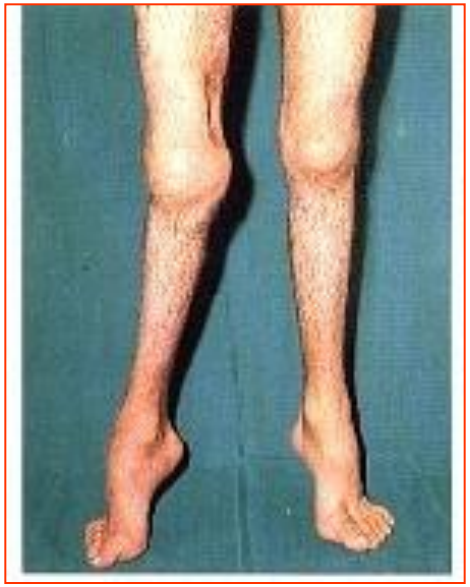






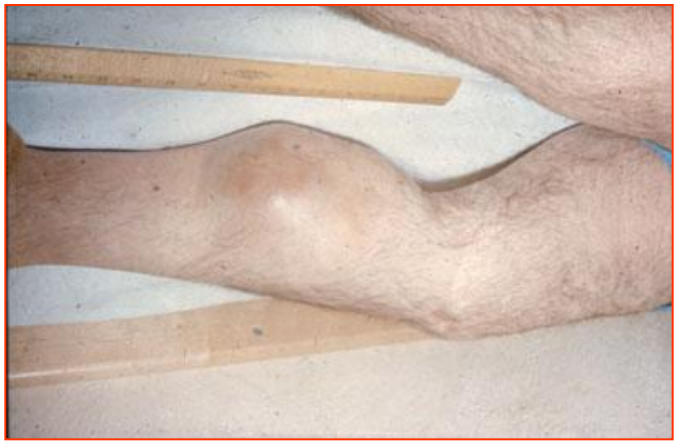


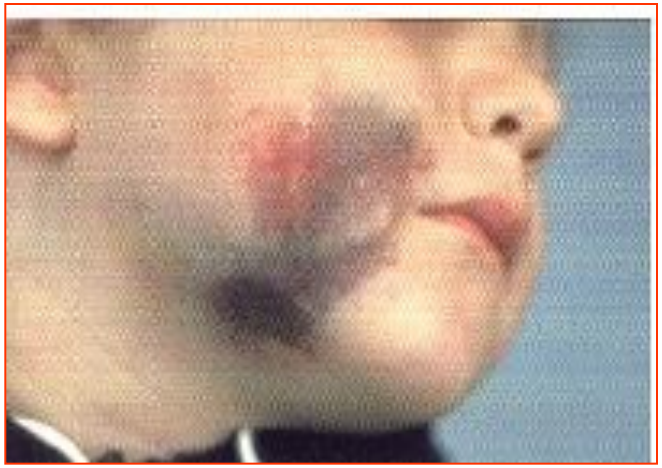


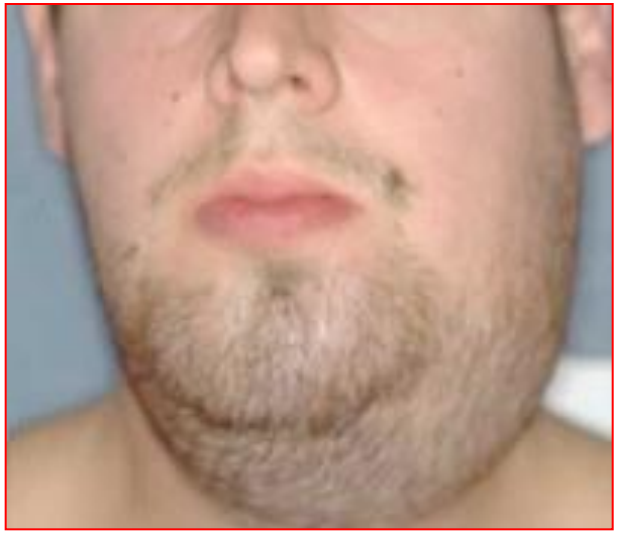


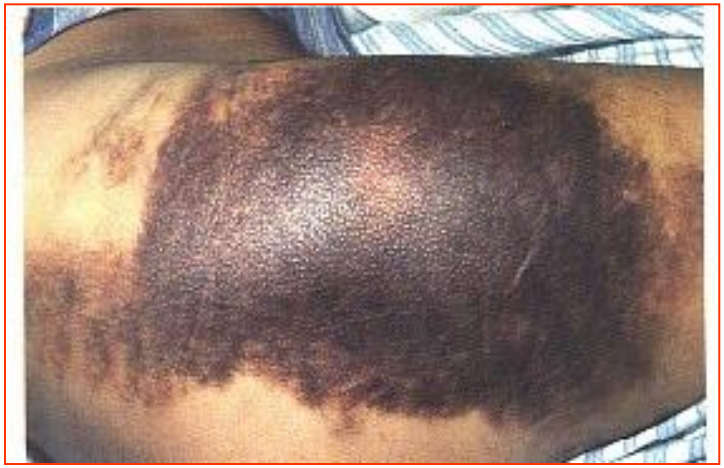
Other types of bleeding:

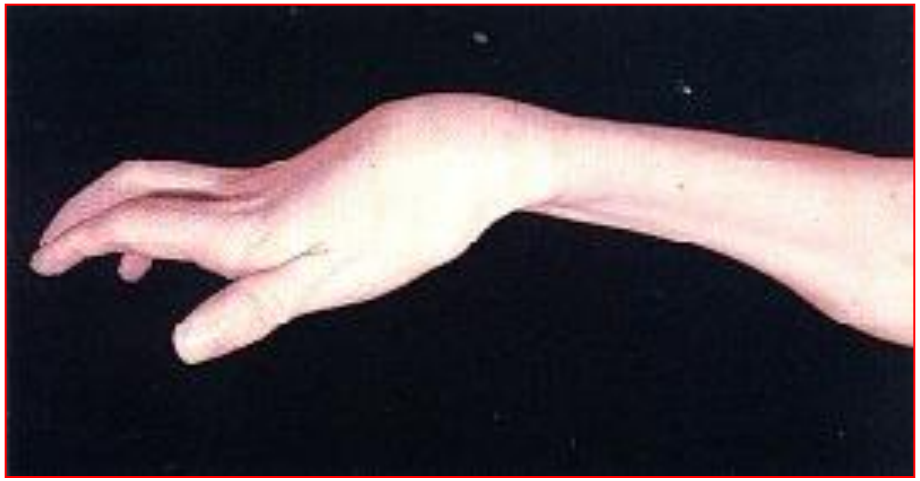
subcutaneous, intramuscular hematomas, gastrointestinal bleeding, hematuria, cerebral hemorrhage







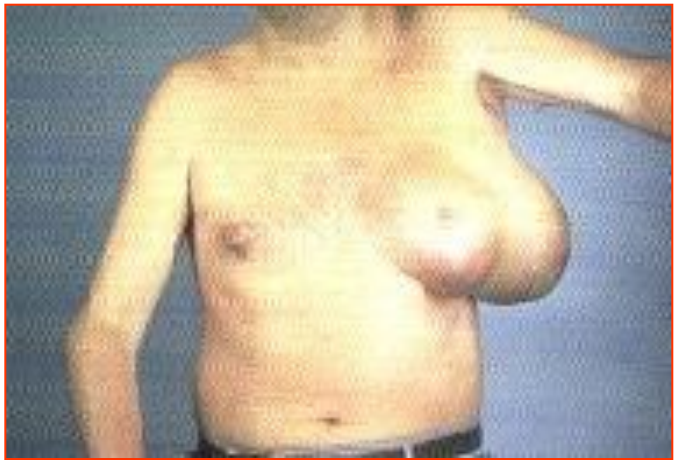


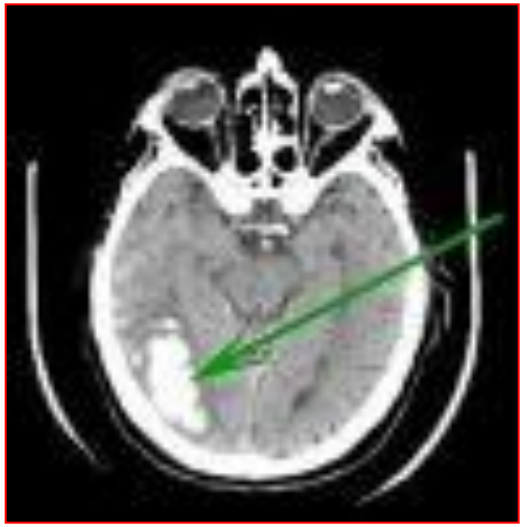


Volkmann's contracture

Large haematoma of the cerebellum
(computer tomography)

Pseudotumor



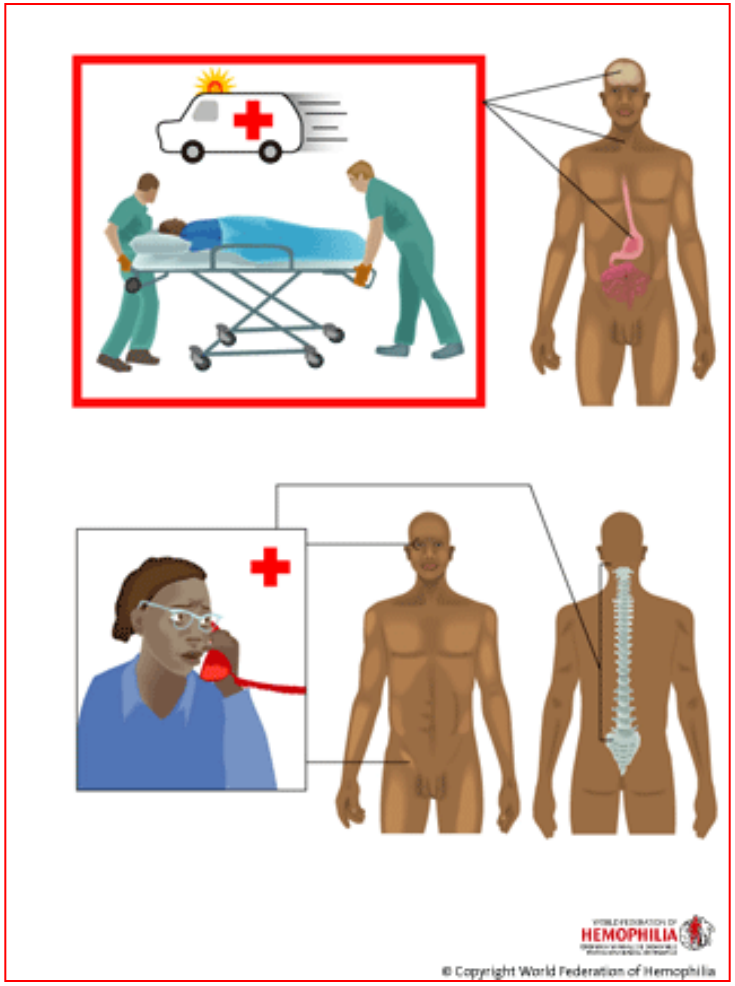


Life-threatening bleeding:

- bleeding within the head is a major cause of death in haemophilia

-Bleeding into the throat may cause swelling, as well as difficulty swallowing and breathing

- Gastrointestinal bleeding (often due to peptic ulceration)



Serious, but usually not life-threatening bleeding:

- bleeds into the eyes, spine and psoas muscle

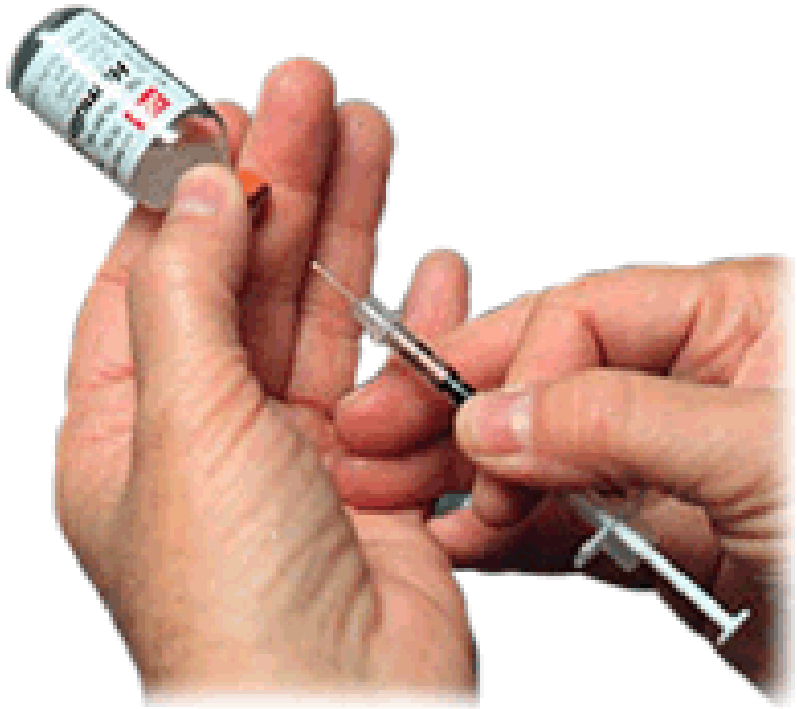
Therapy

The only mode of treatment is replacement therapy: *to inject the missing clotting factor into a vein.*
Clotting factor cannot be given by mouth.

Factor substitution

- **On demand:**
  - **in the event of bleeding episodes**
- **Profilaxis:**

  to prevent bleedings and their consequences
  - **primary**
  - **secundary**
- **Home treatment:**
  - **the patient or his relatives are taught to give iv. injection of the factor concentrate immediately when there are symptoms of bleeding.**



Calculation of the dose of factor replacement

Haemophilia A:

(desired level FVIII % - patient FVIII level %) x bodyweightkg/2

Haemophilia B:

(desired level FIX % - patient FIX level %) x bodyweightkg

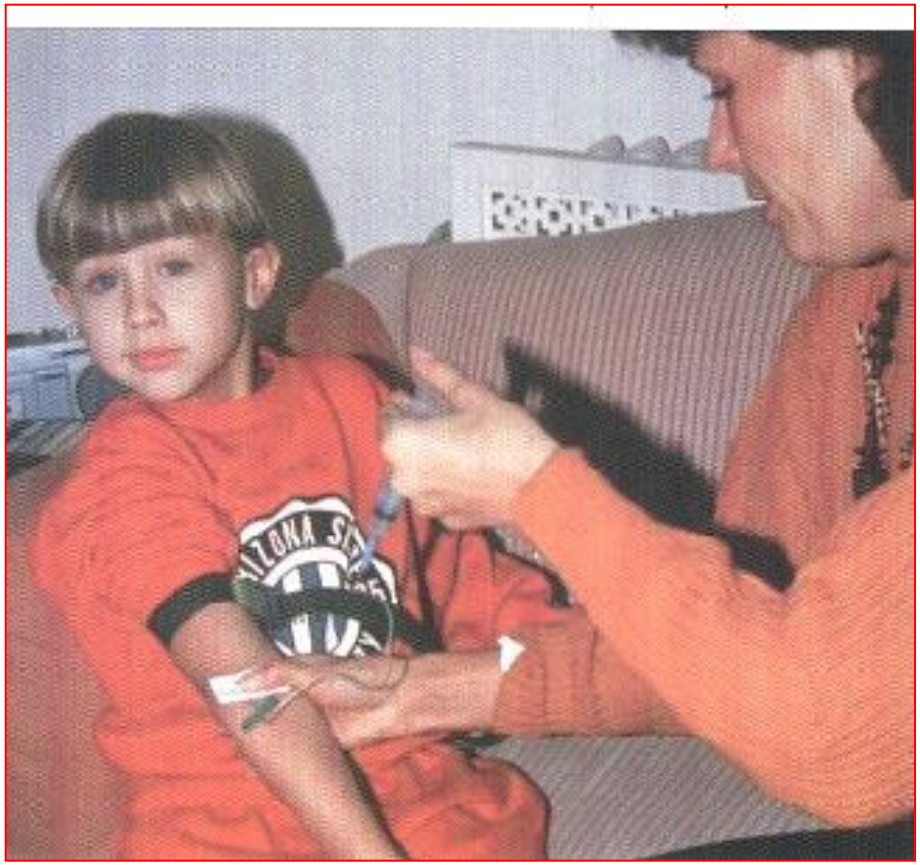
Recommended doses of FVIII/FIX for various types of haemorrhage

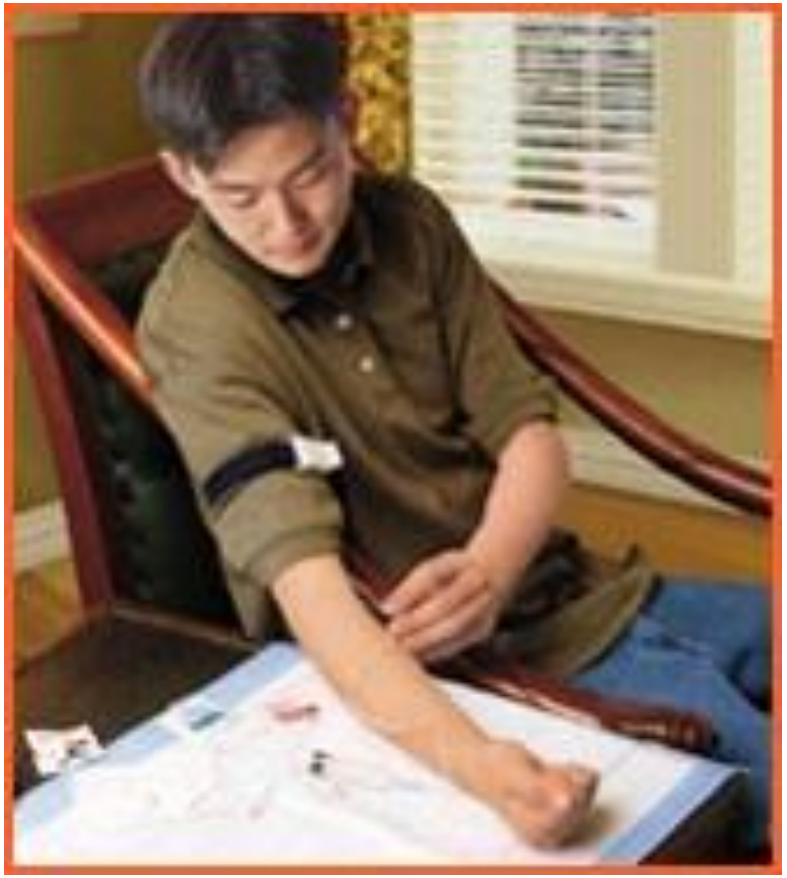
Site of hemorrhage:	Desired FVIII/FIX level (%):	Duration (days):
Hemarthroses, superficial, intramuscular hematoma, im. inj.	10-20 %	1-3
Deep intramuscular haematomas	20-35 %	3-4
Tooth extraction, intraabdominal, intrathoracal bleeds, epistaxis, minor surgery	40-50 %	4-14 until healing
Central nervous system, major surgery	50-100 %	14-21 until healing

Factor replacement
at the consulting room

Home therapy:

is infusion with clotting factor replacement away from the hospital. A person with haemophilia can infuse at home, school, work, or elsewhere.





Medical treatment is only one part of good health.

People with hemophilia should:

- Exercise and stay fit.
- Wear protection that is appropriate for the sport or activity.
- Get regular check-ups that include joint and muscle examination.
- Get all vaccinations recommended, including hepatitis A and hepatitis B protection.
- Maintain a healthy body weight. People who do not exercise are more likely to put on extra weight. A person with hemophilia needs to control his weight so that he does not put extra stress on his joints, especially if he has arthritis.

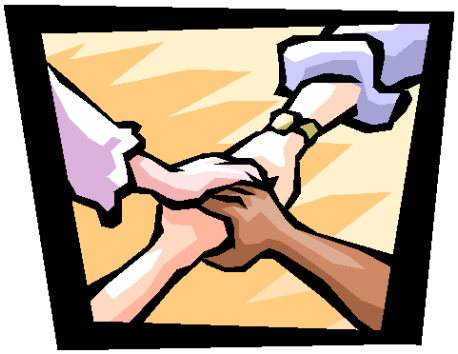
Dental health is very important in haemophilia:

- Healthy teeth and gums reduce the need for haemophilia treatment.

- Regular dental care reduces the need for injections and surgery.

- Dental care should include brushing, flossing, and check-ups by a dentist.

- Cooperation between hematologists (hemostaseologists) and dentists is necessary.

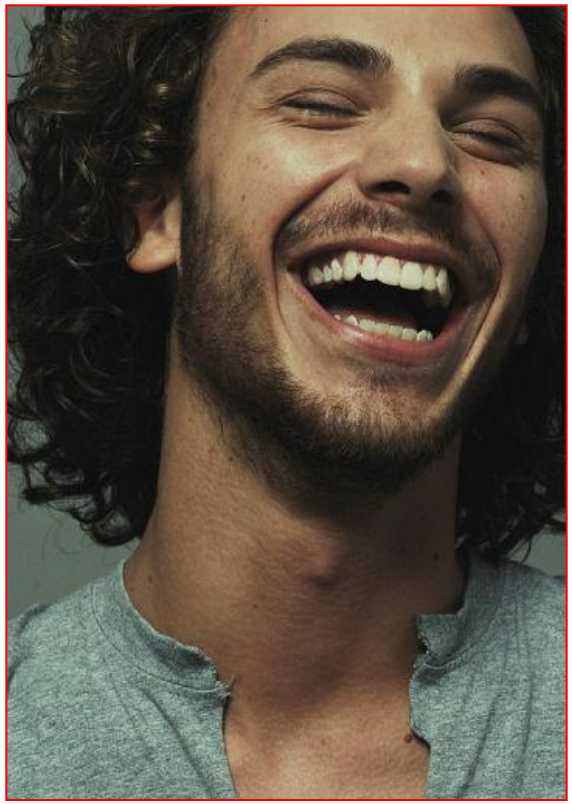


Patients with bleeding disorders need special dental care.

Regular dental visits – usually every 6 months – will help identify problems early.

I. Prevention:

It is an essential component of oral care.
It will reduce the need of treatment and the number of emergency visit.



With prevention

Without prevention

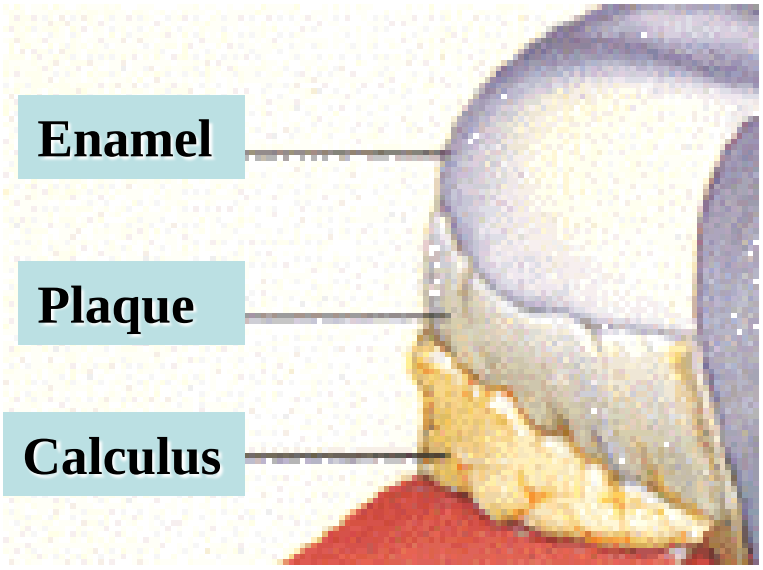
Oral hygiene is very important:

Brushing **twice daily with a fluoride toothpaste.**

Proper brushing is essential for cleaning teeth and gums effectively.

It removes plaque from the surfaces of teeth.

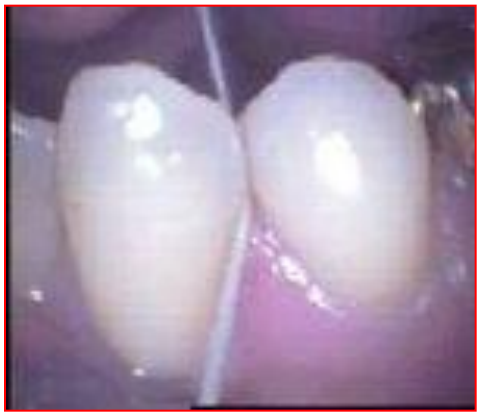
Plaque develops into unhealthy calculus.



Brushing must begin at childhood.

The toothbrush should have medium texture bristles (- hard bristles can cause abrasion of the teeth - soft bristles are inadequate).

Interdental cleaning aids (floss, tape, interdental brushes) should be used to prevent the formation of dental caries and periodontal disease.



Fluoride supplements

(fluorid drops, tablets, topical application of fluorid mouthrinses)
are recommended if the water supply is < 0,6 ppm

Recommended Fluoride Supplementation:

AGE	FLUORIDE ION LEVEL IN DRINKING WATER (ppm)		
	Less than 0.3 ppm	0.3 to 0.6 ppm	More than 0.6 ppm
Birth - 6 months	NONE	NONE	NONE
6 months - 3 years	0.25 mg / day	NONE	NONE
3 - 6 years	0.50 mg / day	0.25 mg / day	NONE
6 - 16 years	1.0 mg / day	0.50 mg / day	NONE

Dietary Counseling

The consumption of food and drinks with a high sugar and acid content should be limited to mealtimes

(the aim: food and drink does not cause the pH level of the oral cavity to fall below the critical level of pH 5,5).

Artificial sweeteners (aspartame, sorbitol, acesulfamate) can be used as an alternative to sugars.

II. Dental treatment

It is essential to prevent accidental damage to the oral mucosa.

Injury can be avoided by:

- careful use of saliva ejectors

- careful removal of impressions

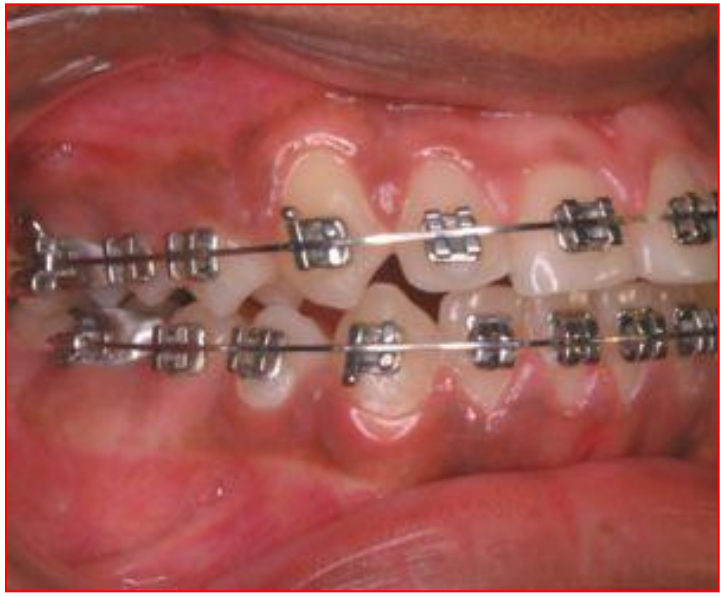
- care in the placement of X-ray films

- protection of soft tissues during restorative treatment.

Orthodontic treatment:

Fixed and removable orthodontic appliences may be used.

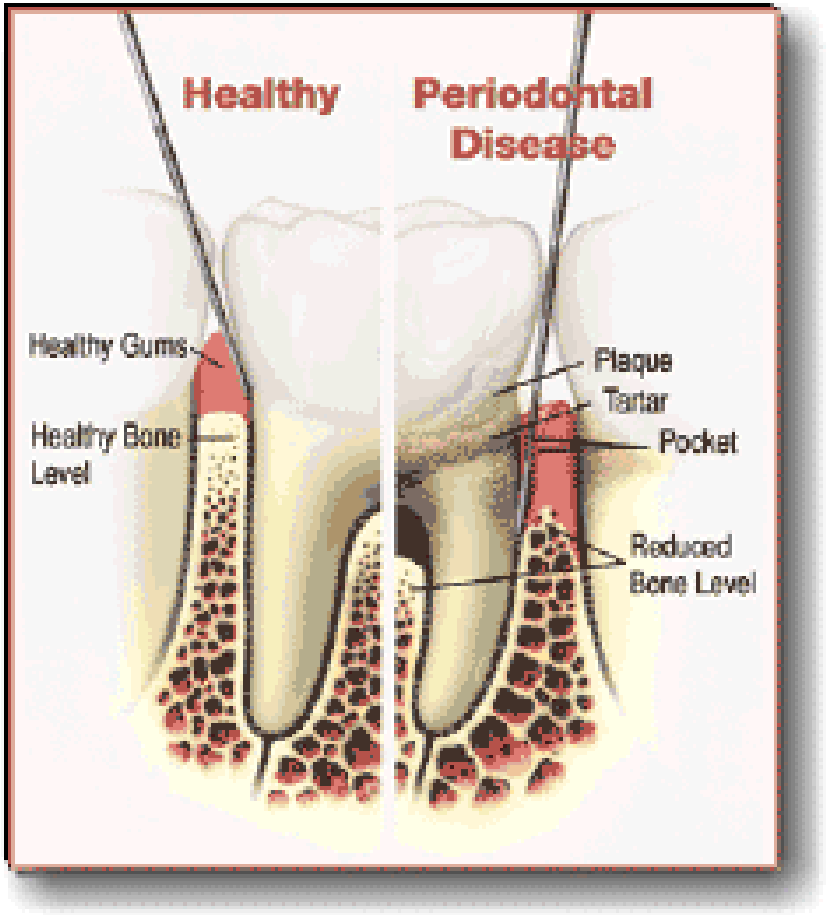
Special care should be taken when treating patients with a severe bleeding disorder to ensure that the gingiva is not damaged when fitting the applience.



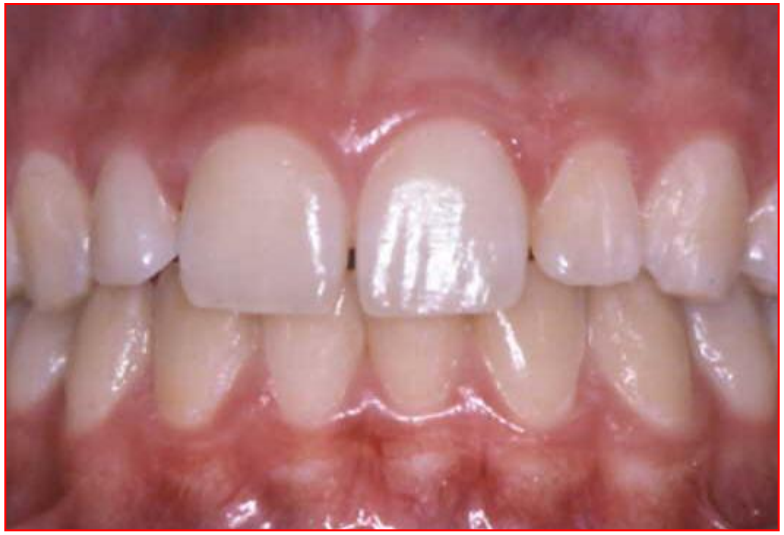
Periodontal treatment:

GUM DISEASE IS THE MAIN CAUSE OF TOOTH LOSS!

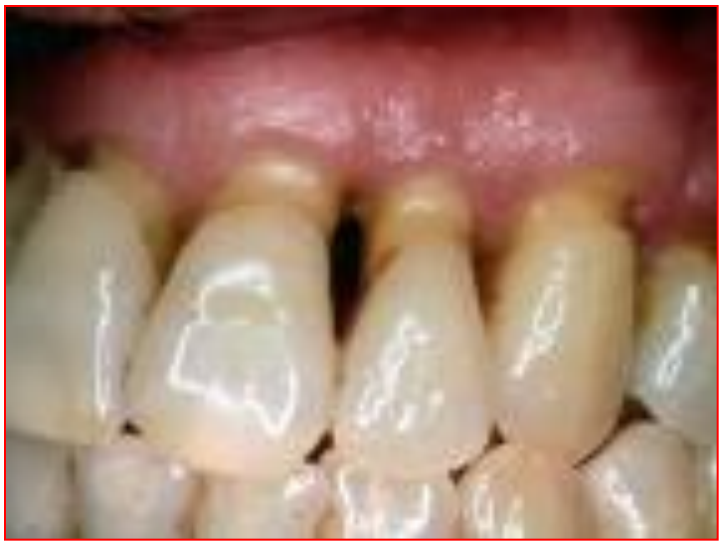
Mouth tissues reflect symptoms of other problems.
80 % or more of adults have some form of periodontal disease and
99% of those have no signs that indicate they have a problem.



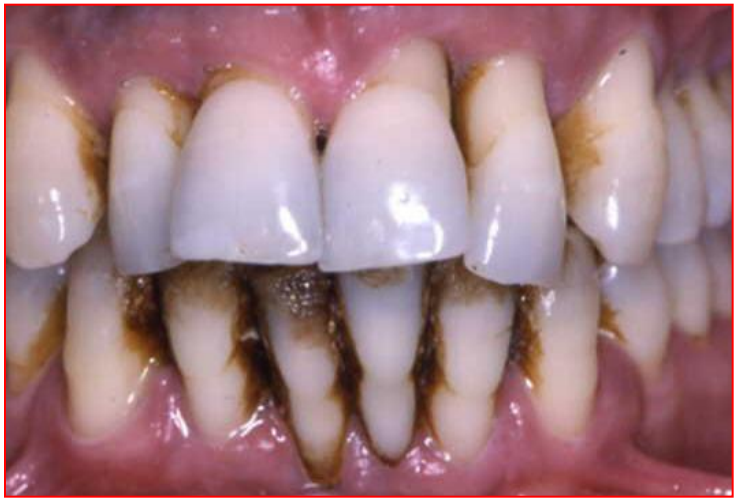
Healthy gums



Periodontitis (gum disease)



Severely advanced periodontal (gum) disease, with receded gums, massive stains from smoking cigarettes and inadequate oral hygiene.



In case of periodontal disease treatment must start as soon as possible.

Factor replacement therapy is not necessary.

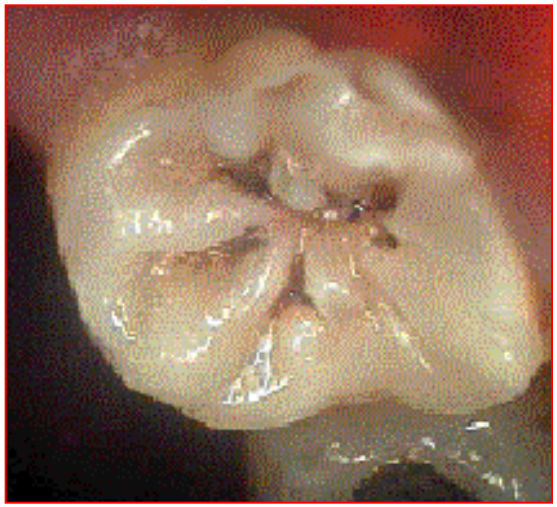
Bleeding can be controlled locally: with direct pressure and topical antifibrinolytic agents.

Clorhexidine gluconate mouthwash can be used to control periodontal problems.

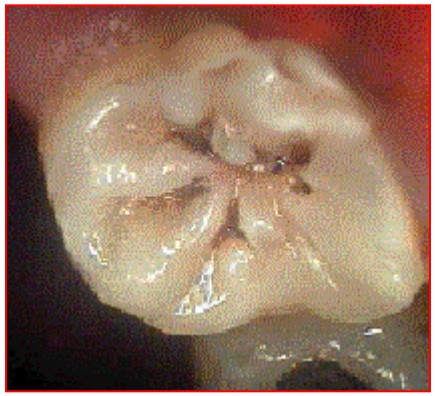
Antibiotics may be required to help reduce the initial inflammation.

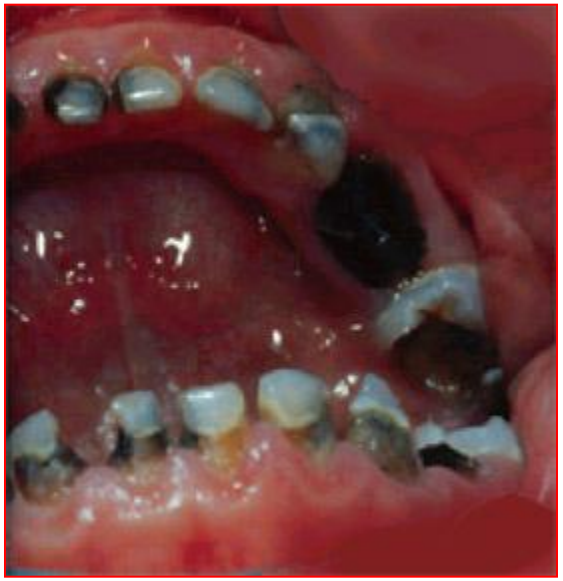
Dental caries

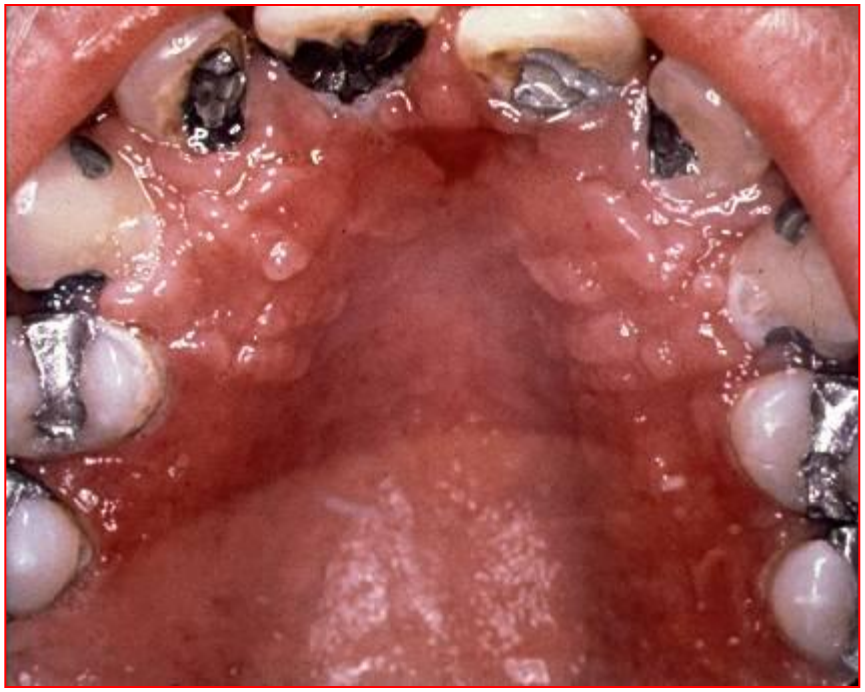
- **If the oral hygiene is bad, certain bacteria have overgrown on certain parts of the tooth surface and have produced so much acid that the tooth mineral has dissolved or decayed, forming a cavity.**

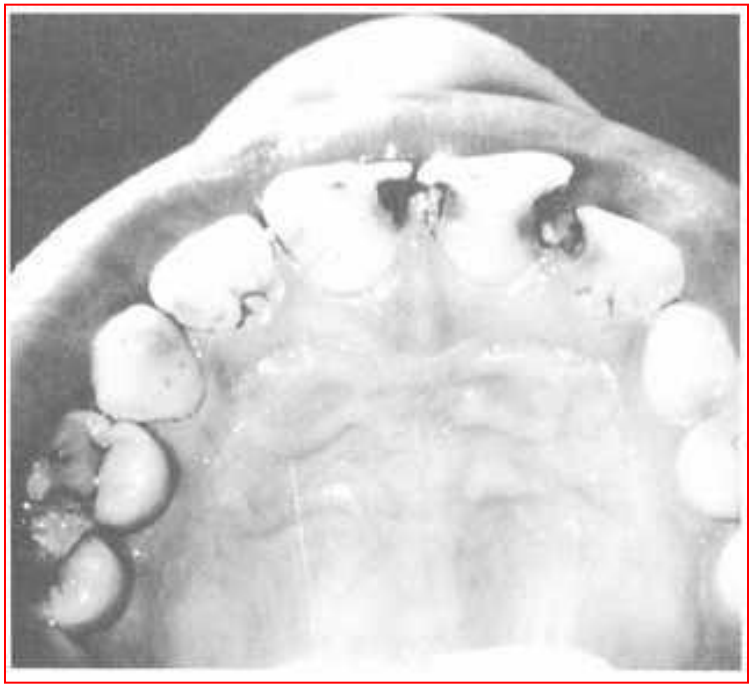


Carious lesions





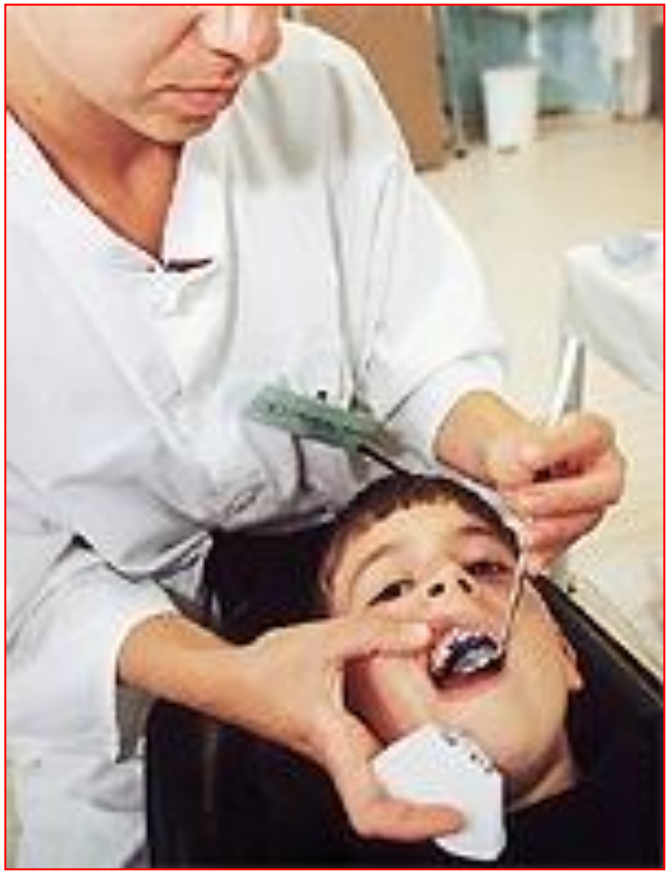




Restorative treatment:

Filling a cavity can be undertaken routinely with protection the mucosa.

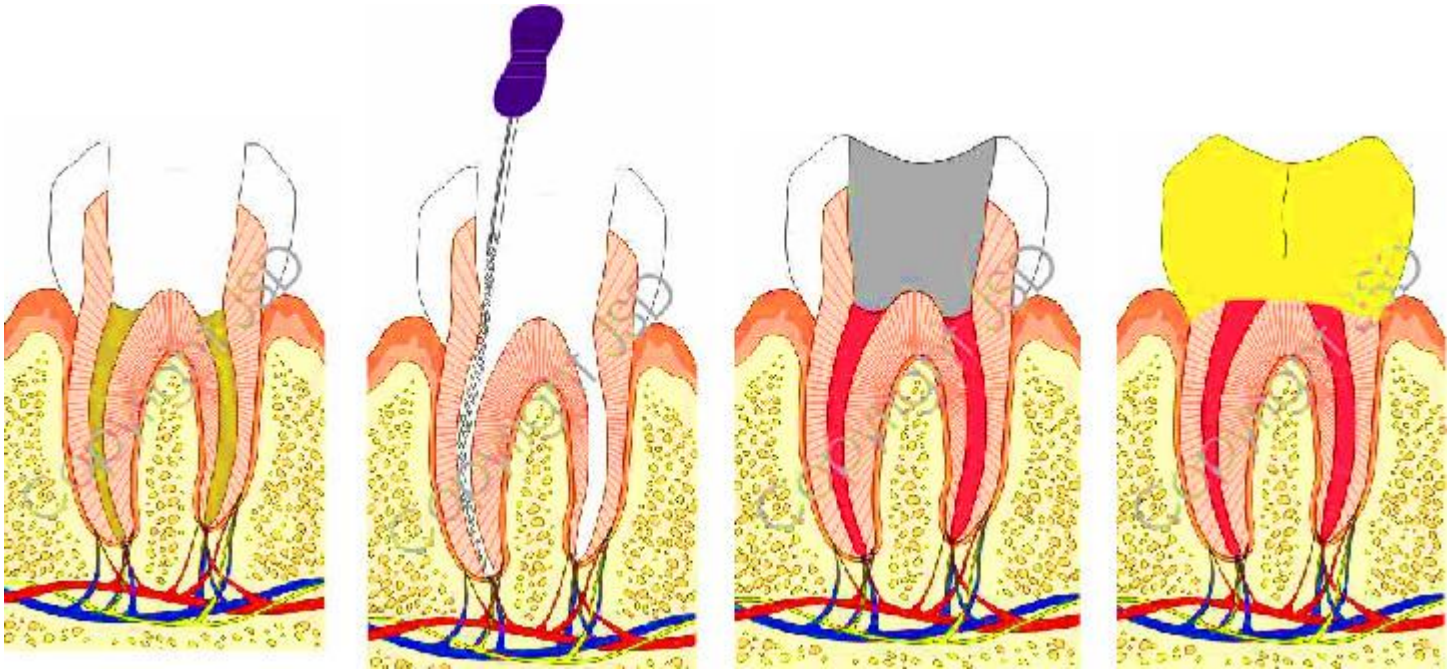
In the case of local anesthesia factor replacement therapy is necessary.



Endodontic treatment (root canal therapy):

It is generally low risk for patients with bleeding disorders.

Pulpectomy be carried out carefully (the instrument do not pass through the apex of the root canal).



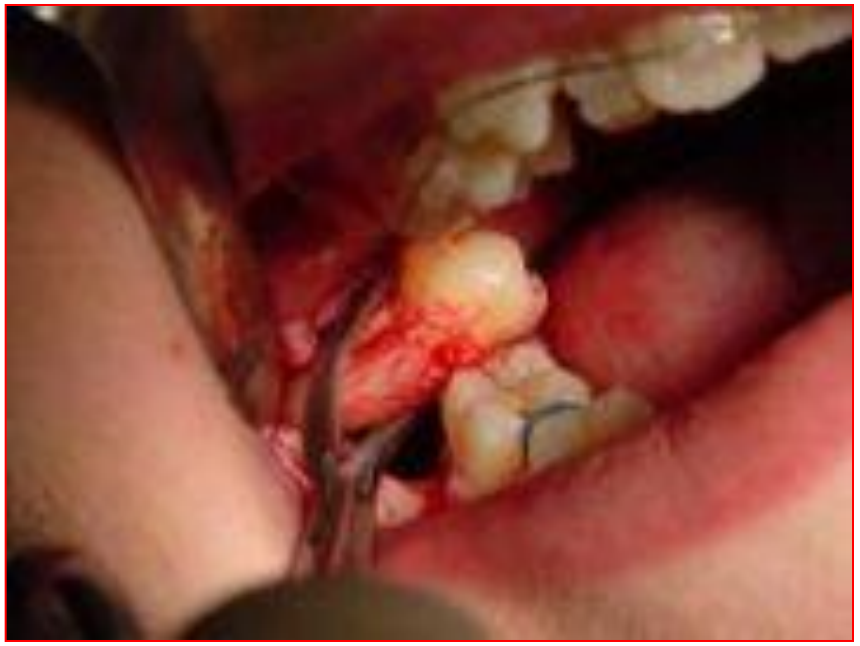
Tooth extraction, dental surgery:

Extraction of even a single tooth requires replacement therapy (recommended FVIII/IX level: 40-50 %).

Multiple extractions may save time and expense but create a major bleeding hazard.

The suturing of bleeding tooth sockets should be avoided.

Antifibrinolytics (tranexamic acid = Exacyl) may diminish bleeding in patients with coagulation disorders.



Anesthesia and pain management:

- Minor analgesics:

dental pain can be controlled with a minor analgesic, such as paracetamol. *Aspirin should not be used* due to its inhibitory effect on platelet function!

- Local anesthesia:

No haemostatic cover:	Haemostatic cover required:
Buccal infiltration	Inferior dental block
Intra-papillary injection	Lingual infiltration
Intraligamentary injections	

Guidelines for Dental Treatment of Patients with Inherited Bleeding Disorders (WFH, Dental Committee, 2006)

Inferior alveolar nerve block:

It is a risk of bleeding into the muscles along with potential airway compromise due to a haematoma in the retromolar or pterygoid space.

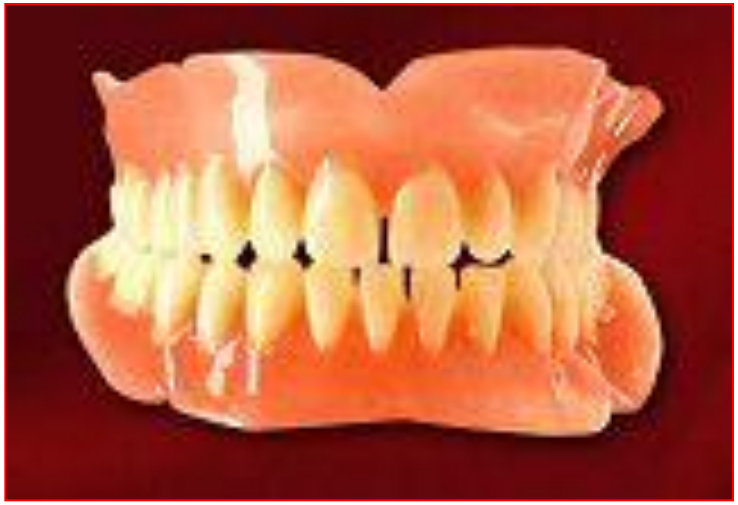
A lingual infiltration:

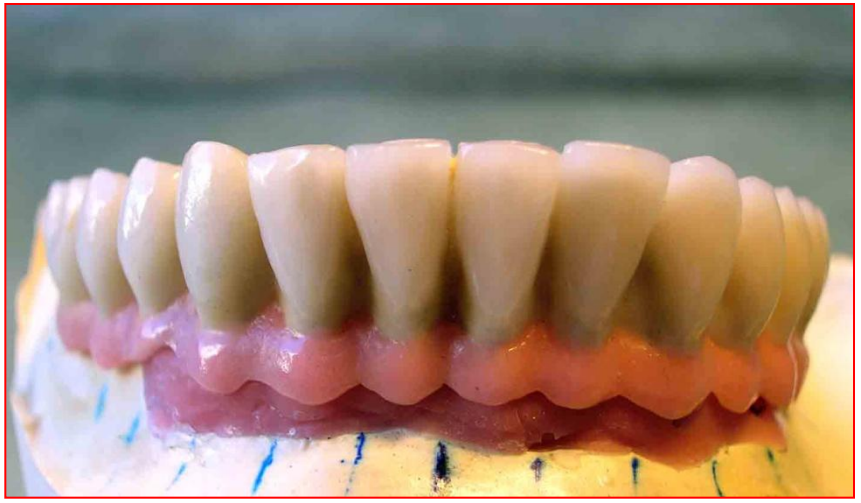
There is a risk of a significant airway obstruction in the event a bleed.

Dental prosthesis

Patients with bleeding disorders can be given dentures.

If a partial denture is provided it is important that the periodontal health of the remaining teeth is maintained.

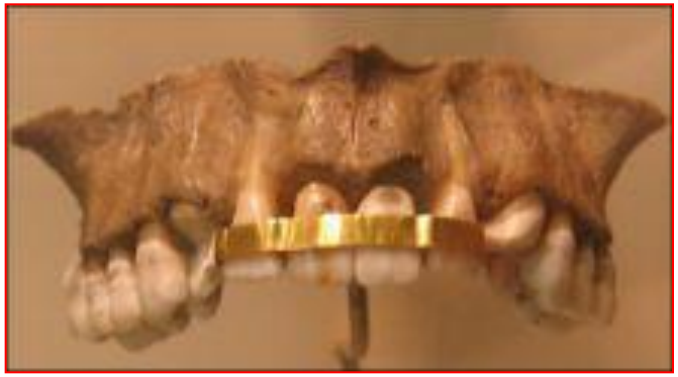




The earliest known dental prosthesis from Rome ***(date from the 1st to the 2nd century A.D.)*** **resulted from multi-karat gold wire, which was used to string together "artificial teeth."**

They were found in the mouth of ***an unidentified woman*** **who was buried in an elaborate mausoleum within a Roman necropolis.**

It is believed the unidentified Roman's bridgework was made from the woman's own teeth that probably fell out due to periodontal disease. Gold wire bound the teeth together.



In dental health of a patient with bleeding disorder team work is very important

(patient- dentist- haematologist)