Hemorrhagic coagulation disorders

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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 coagulation mechanism (*„coagulopathies”*)**

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: -
- 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)

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.**

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

Hemophilia

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

Prevalence:

hemophilia A: 105/million men

hemophilia B: 28/million men

Hemophilia was known to the ancient world.
The earliest written references to what appears to be hemophilia are encountered in Jewish texts (Talmud) of the second century AD.
Rabbinical rulings exempted male boys from circumcision if two previous brothers had died of bleeding after the procedure.

The first modern description of hemophilia is attributed to Dr. John Conrad Otto, a physician in Philadelphia, who in 1803 published a treatise entitled "An account of an hemorrhagic disposition existing in certain families."

„It is a surprising circumstance that males only are subjects to this affliction (hemorrhagic disposition)". Although females are exempt, they are still capable of transmitting it to their male children".

(J. C. Otto, 1803)

Hemophilia has often been called the "Royal Disease." Queen Victoria of England (1819-1901) was a carrier of the hemophilia gene and subsequently passed the disease on to several royal families.

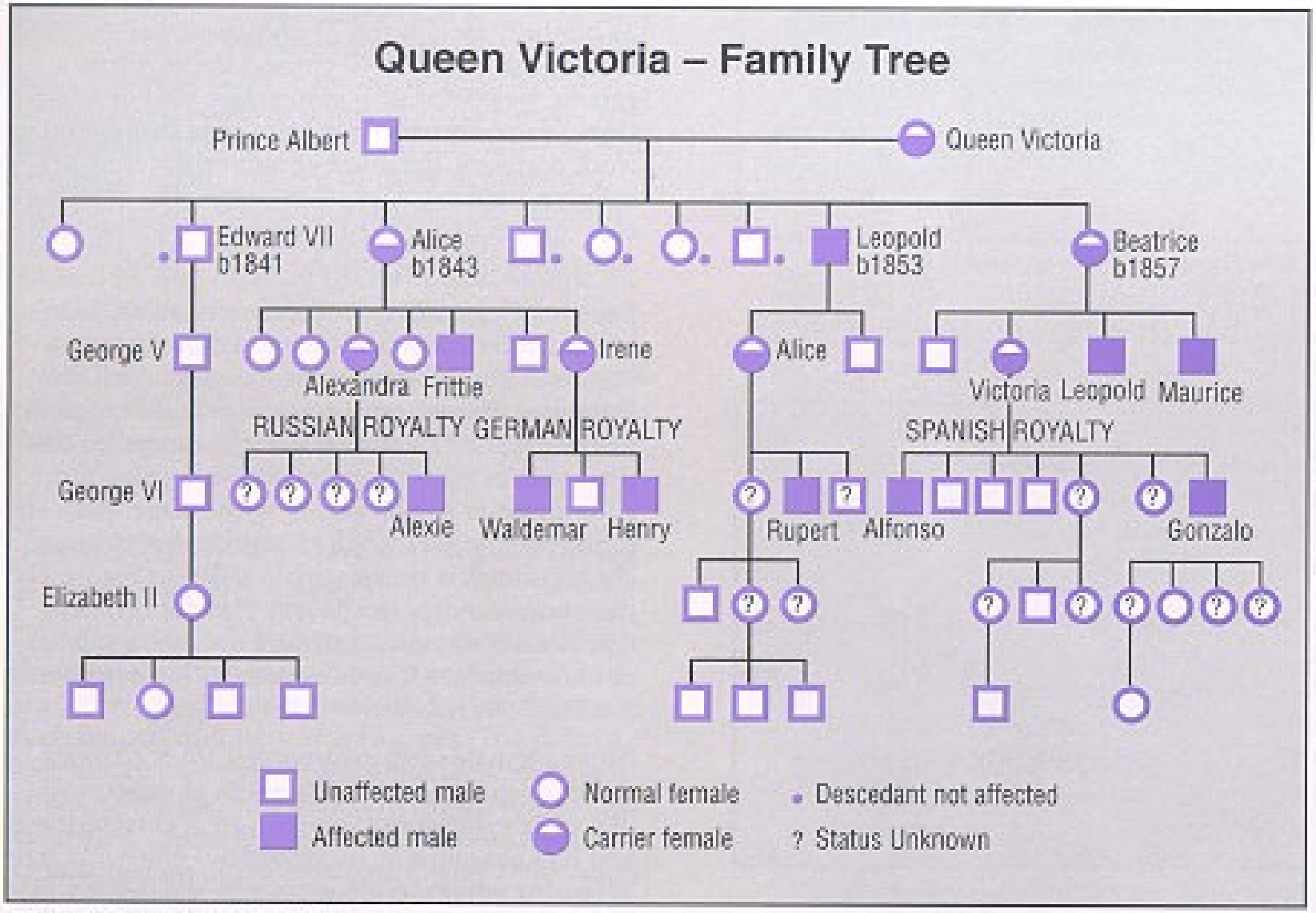


Figure 1. Queen Victoria's family tree.

That the clinical disease is due to abnormalities in two distinct proteins was recognized in 1953 with the identification of FIX by Biggs and McFarlane.

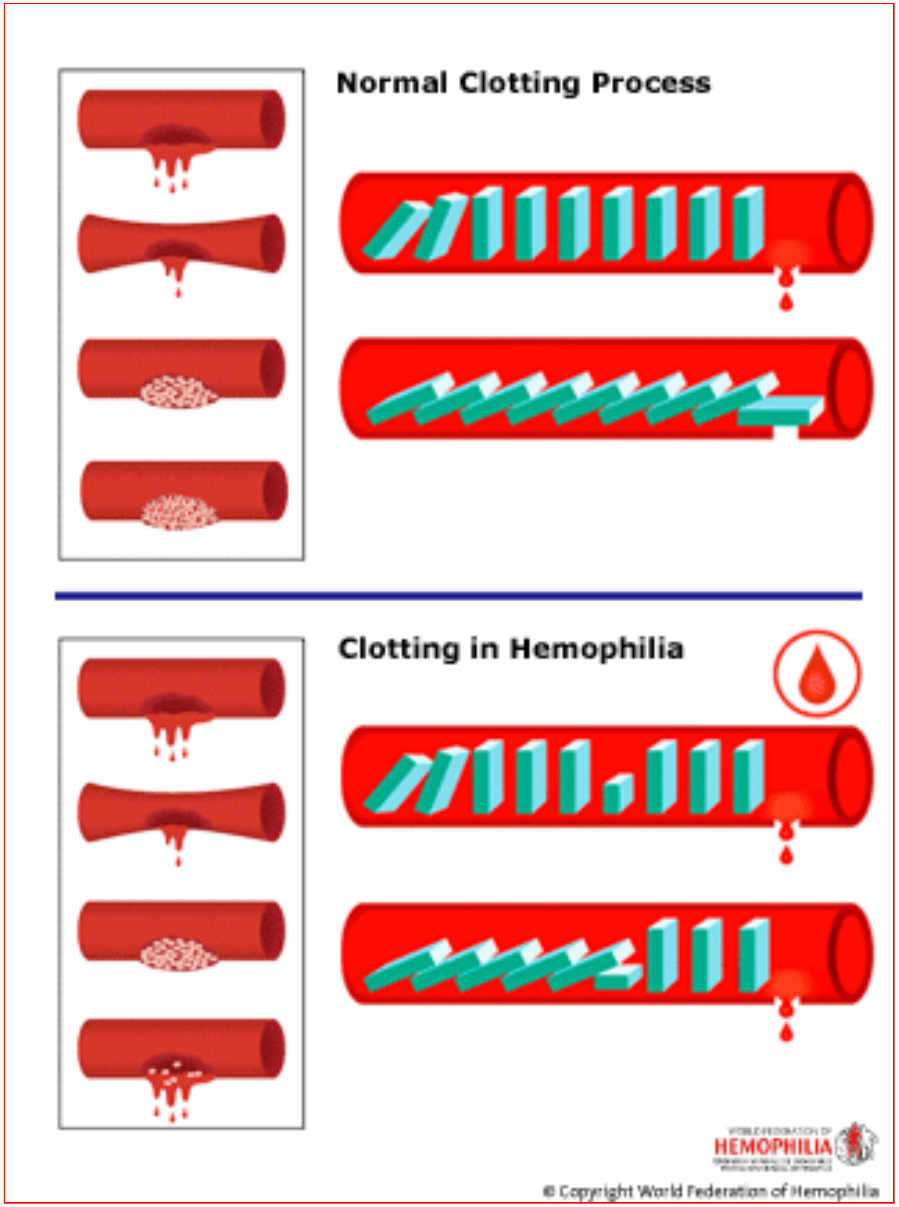
Robert G. Macfarlane
(1907-1987)

Rosemary Biggs
(1912-2001)

Pathophysiology:

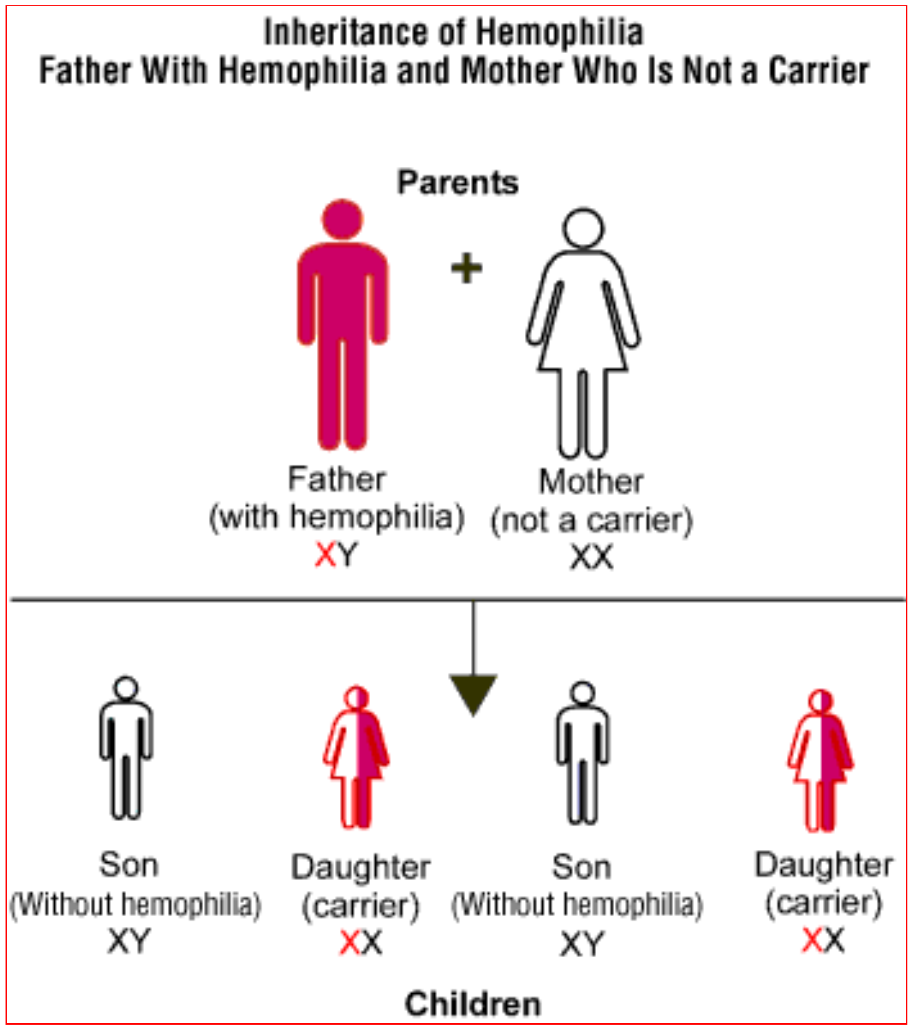
- **In hemophilia, VIII or IX clotting factor is missing, or the level of that factor is low.**

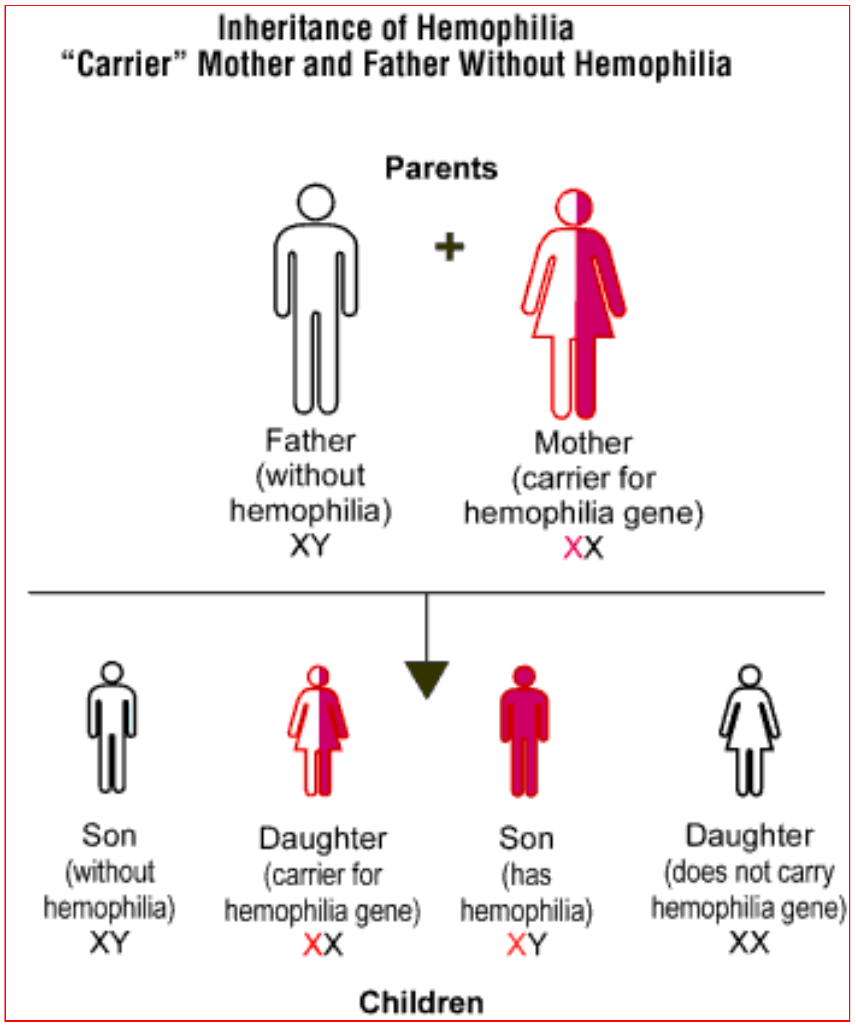
- **This makes it difficult for the blood to form a clot, so bleeding continues longer than usual.**



The hemophilia gene is carried on the X chromosome

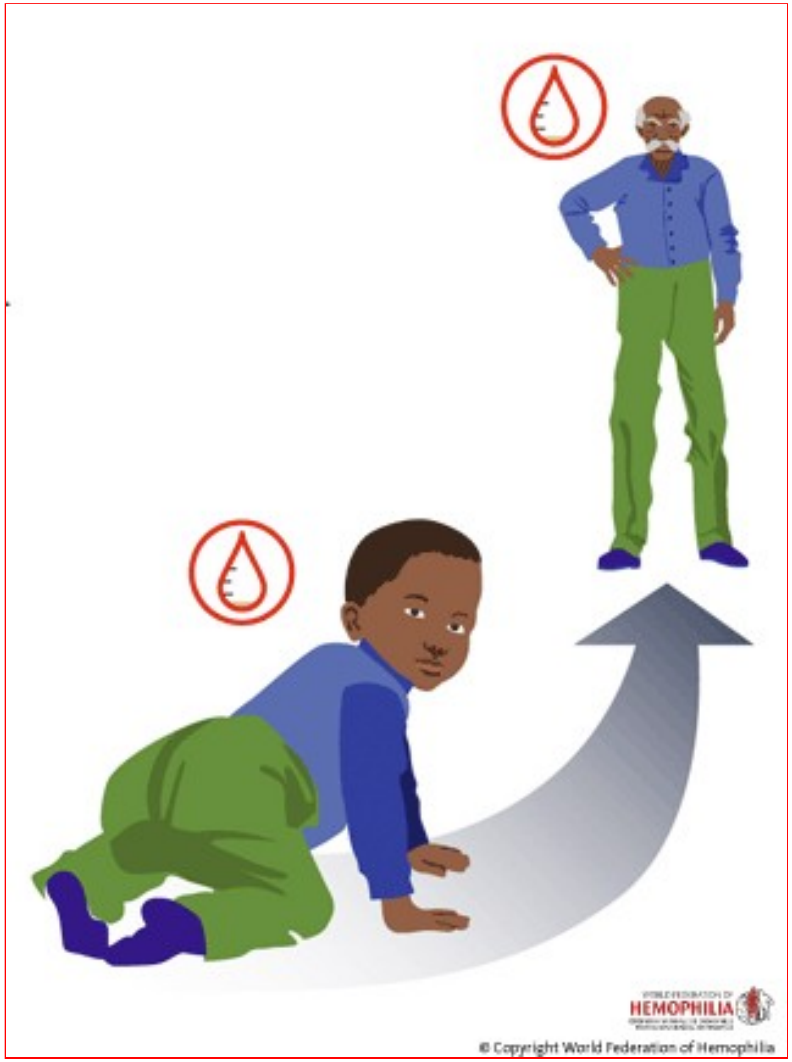
⇒ in males who lack a normal allele, the defect is manifested by clinical hemophilia. Women may be carriers.





Hemophilia is a lifelong disease

- A person born with hemophilia 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 hemophilia 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.

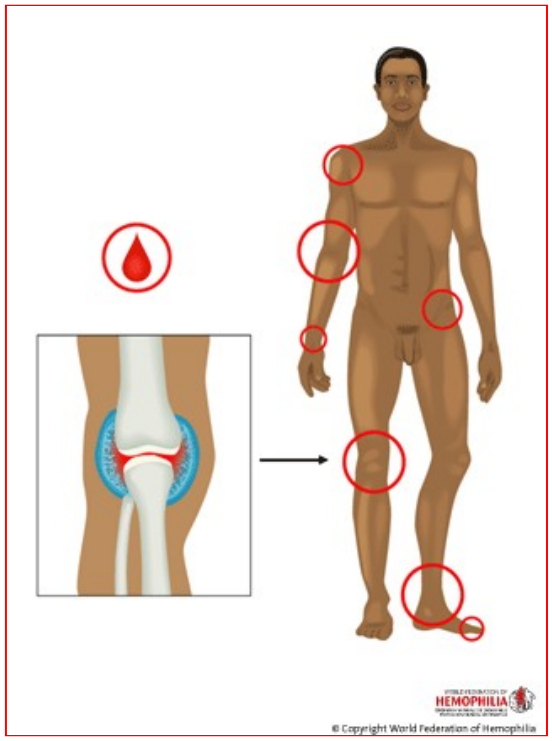
Hemophilia can be mild, moderate, or severe, depending on the level of clotting factor. Three category of severity:

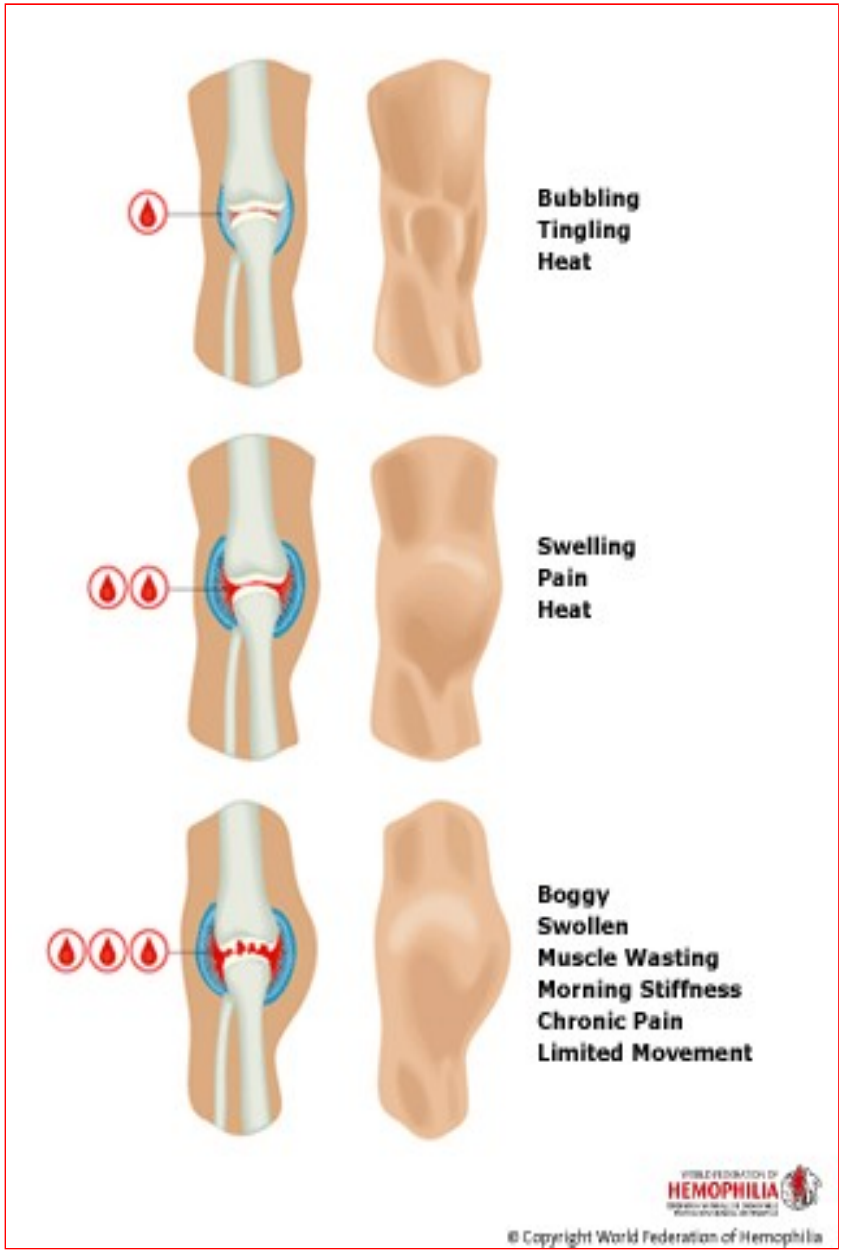
- **Severe: FVIII/FIX < 1 %**
  - Repeated and severe hemarthroses and spontaneous bleeding, crippling common.
- **Moderate: FVIII/FIX: 1-5 %**
  - Spontaneous bleeding and hemarthroses infrequent. Serious bleeding from trivial injuries.
- **Milde: FVIII/FIX: 5-40 %**
  - Spontaneous bleeding manifestations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

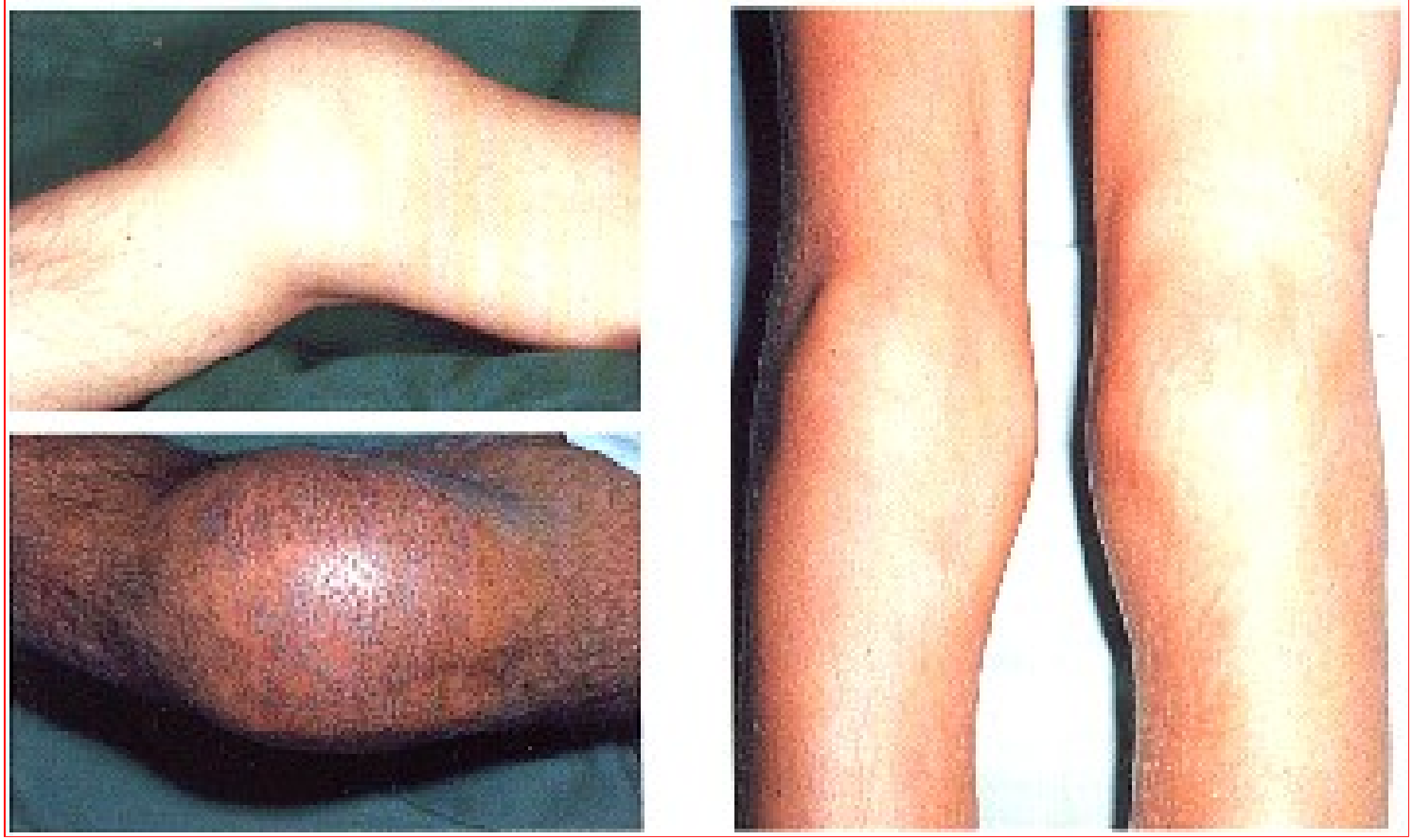
Joint bleeding

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.

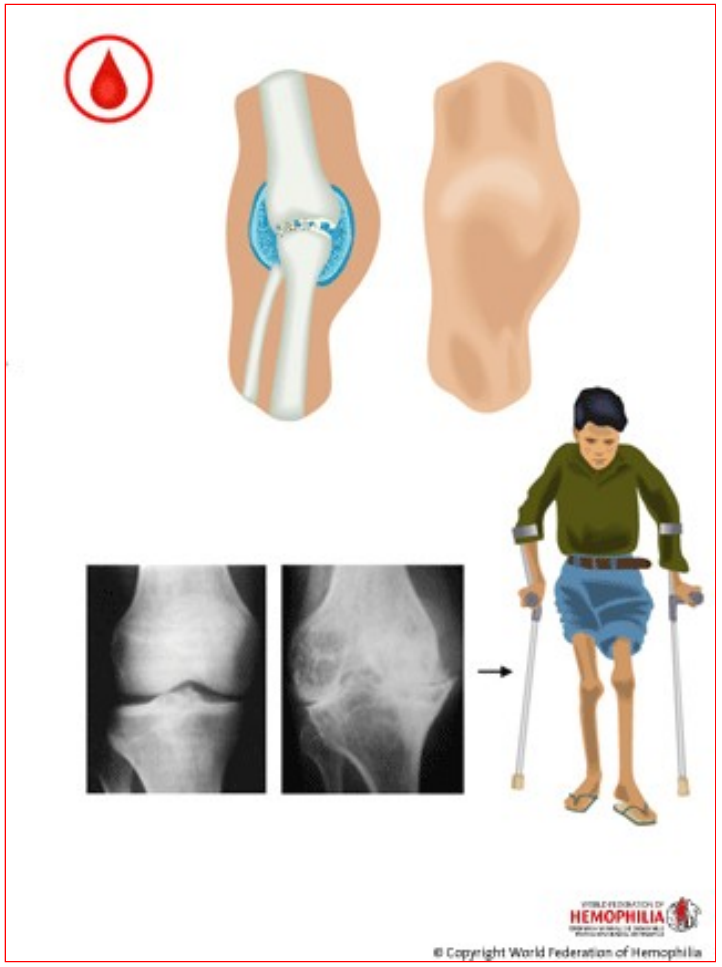






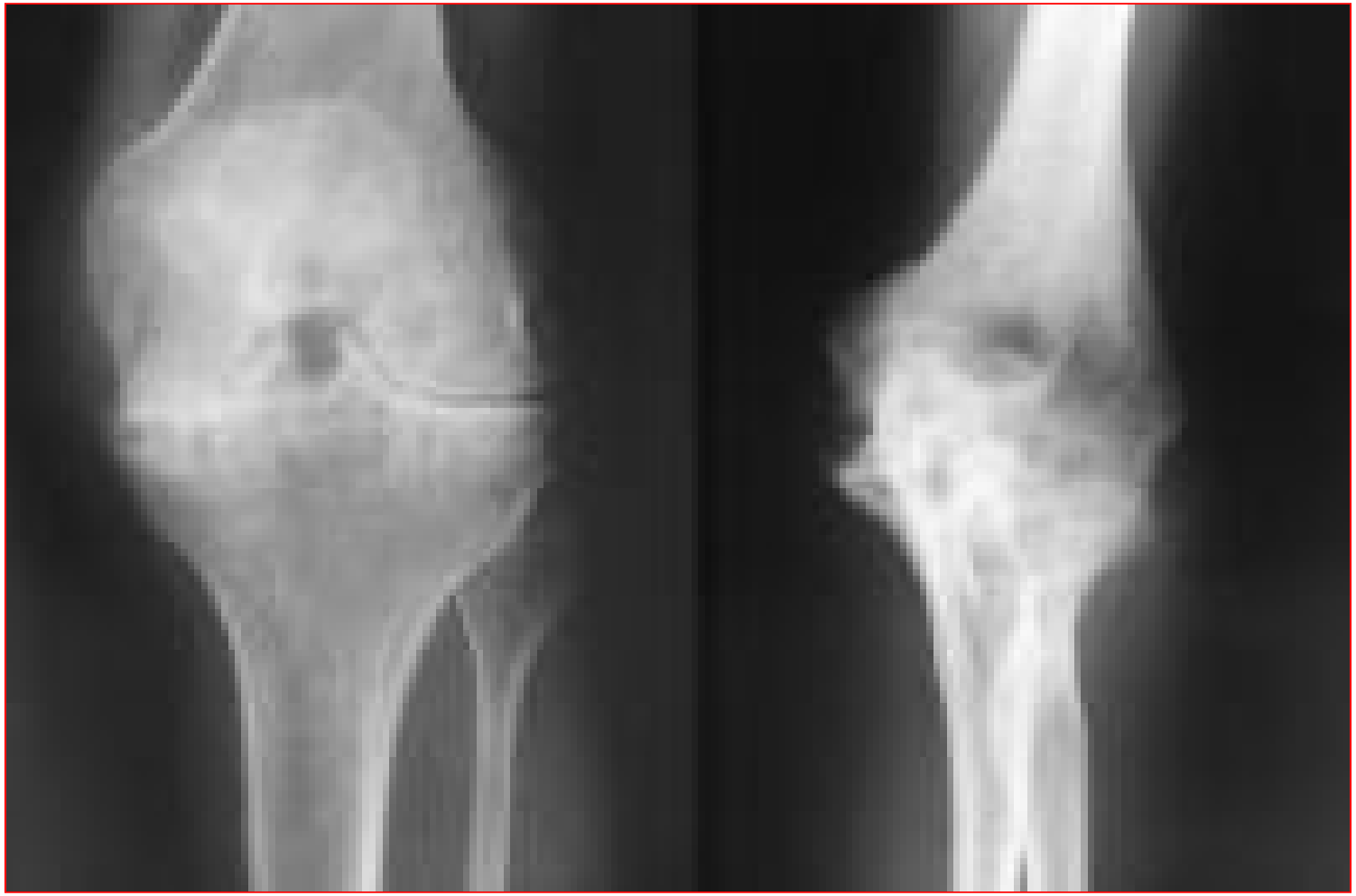
The long-term effects of joint bleeds:

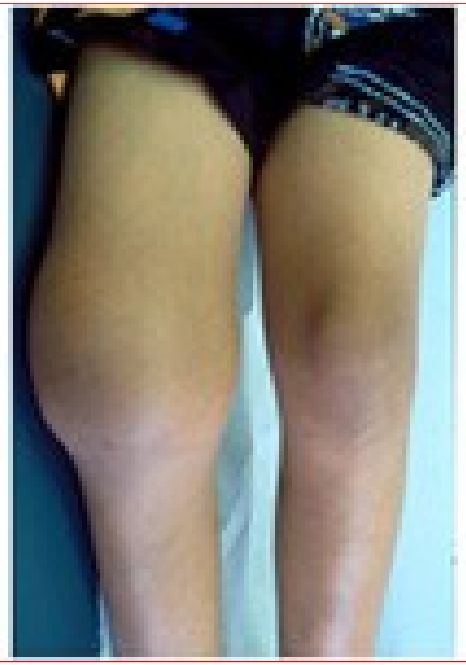
Repeated bleeding into a joint causes the synovium to swell and bleed very easily.
Some blood remains in the joint after each bleed. The synovium stops producing the slippery, oily fluid that helps the joint move.
This damages the smooth cartilage that covers the ends of the bones. The joint becomes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

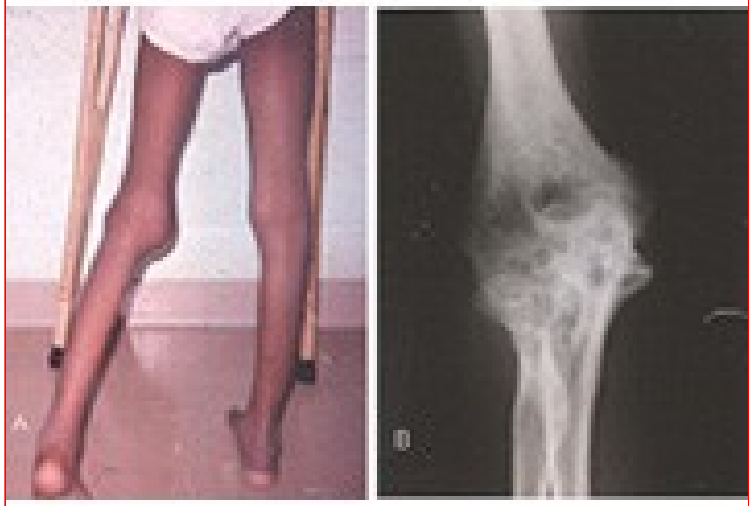


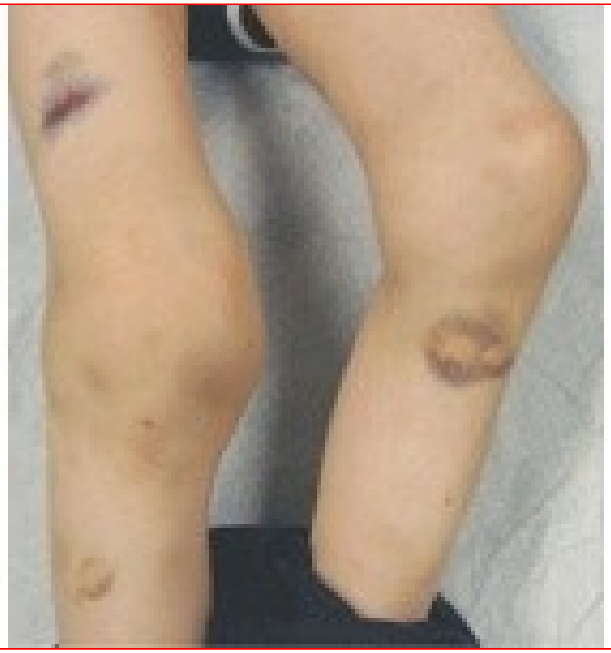
The whole process is called:
hemophilic arthritis.

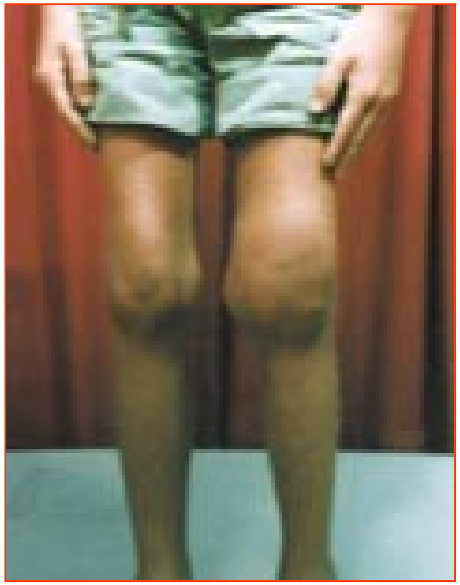
Hemophilic arthropathy (radiographs)

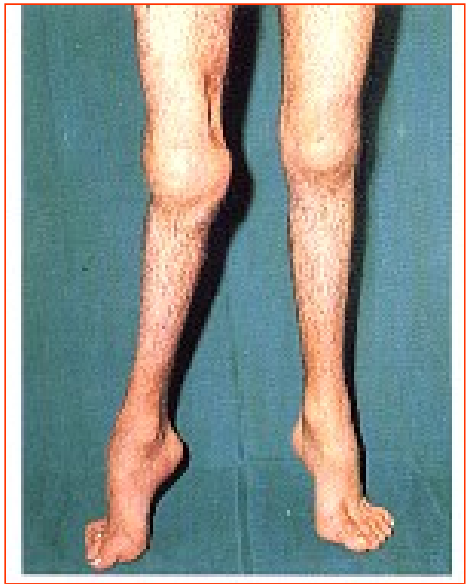





A
B

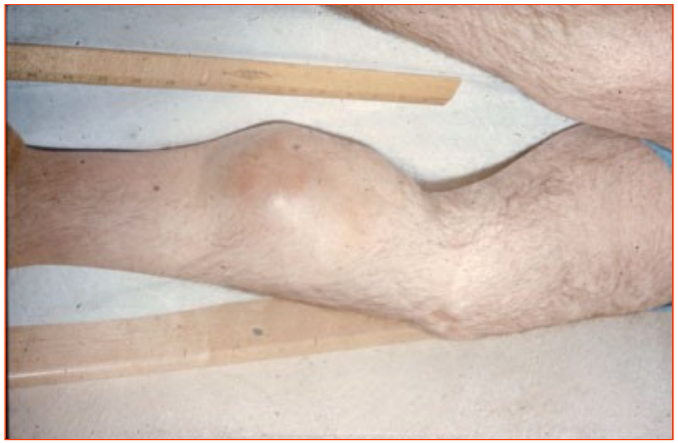


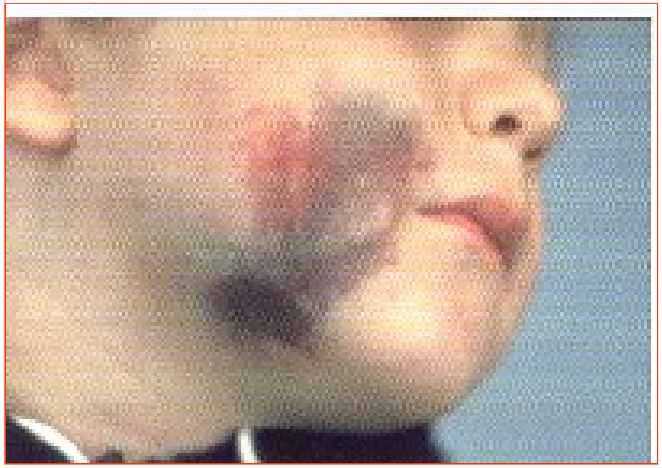


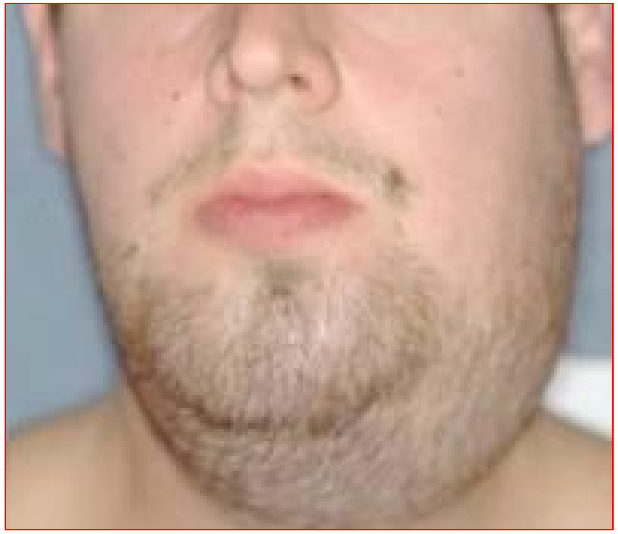


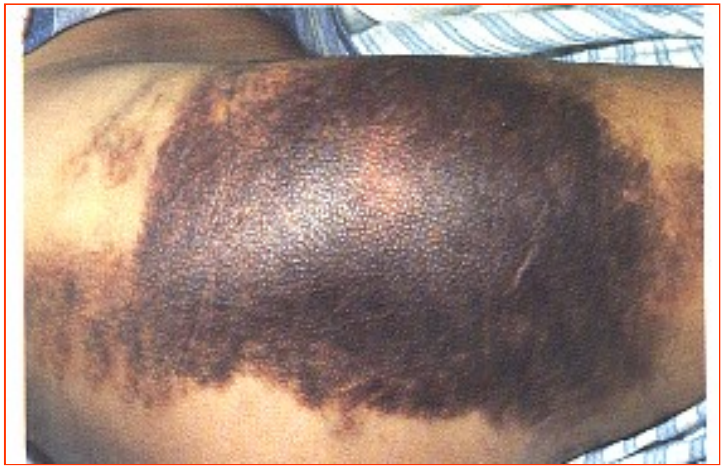
Other types of bleeding:

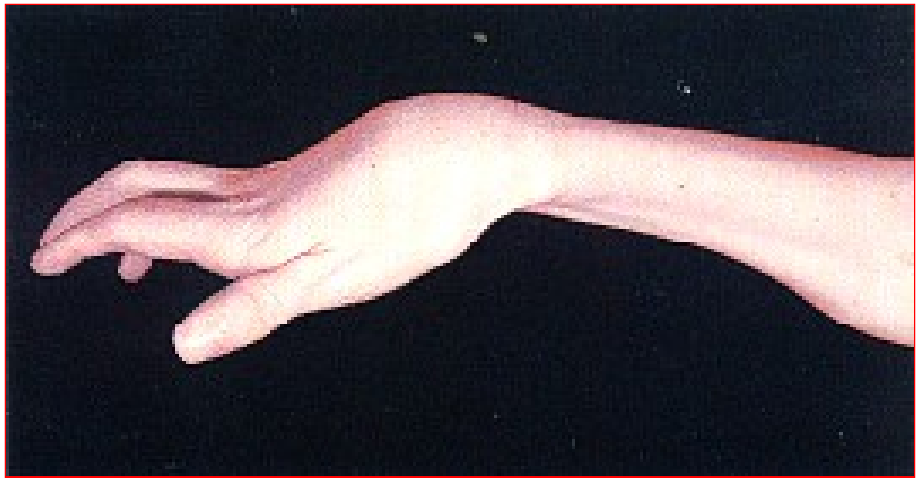
subcutaneous, intramuscular hematomas, gastrointestinal bleeding, hematuria, cerebral hemorrhage







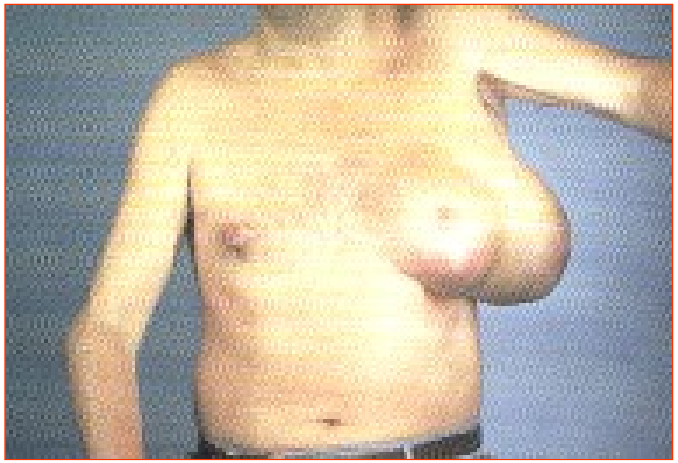


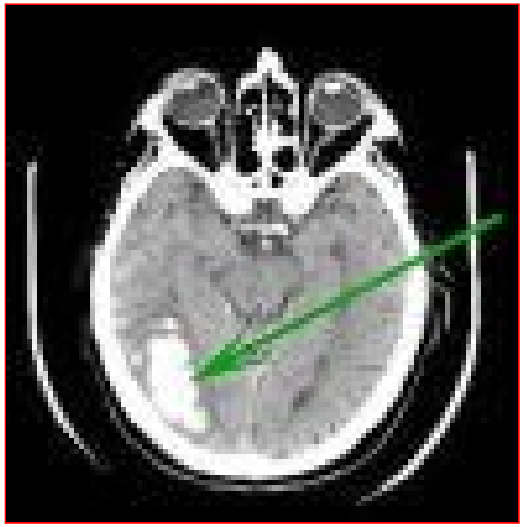


Volkmann's contracture

Large haematoma of the cerebellum
(computed tomography)

Pseudotumor





Life-threatening bleeding:

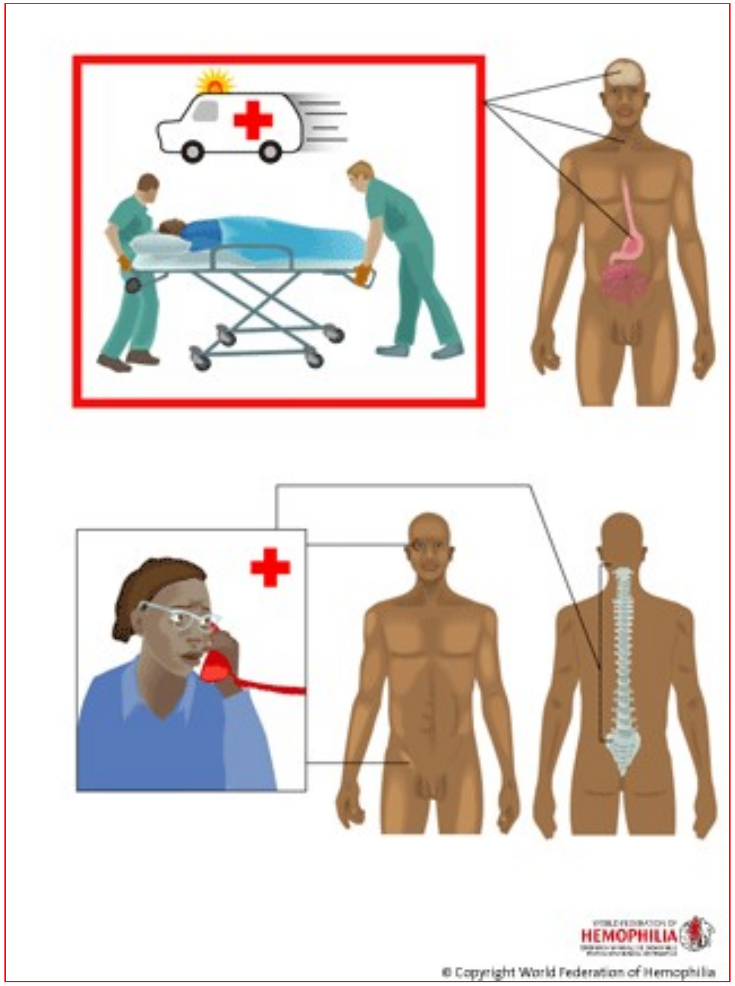
- bleeding within the head is a major cause of death in haemophilia

-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

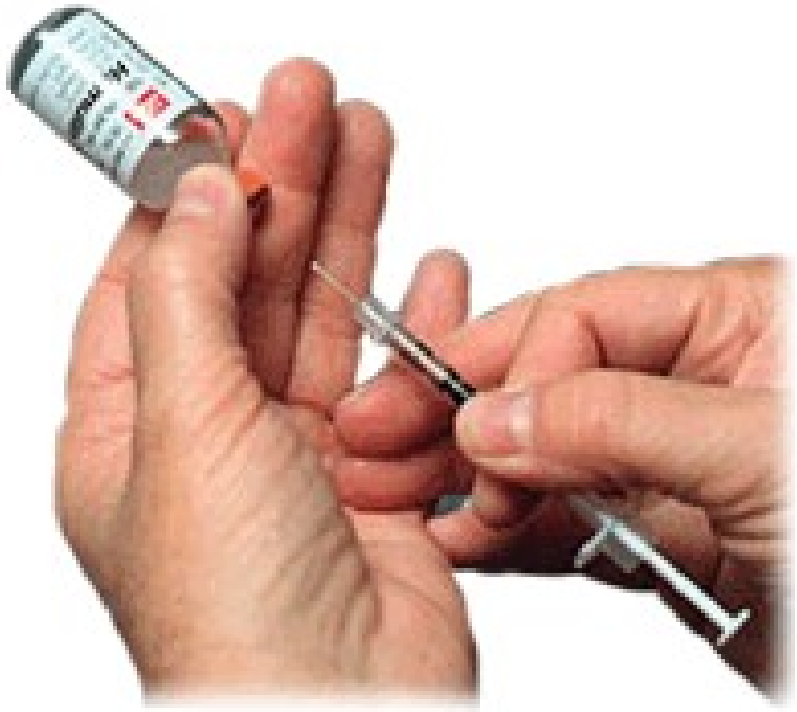


Therapy

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

Hemophilia A:

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

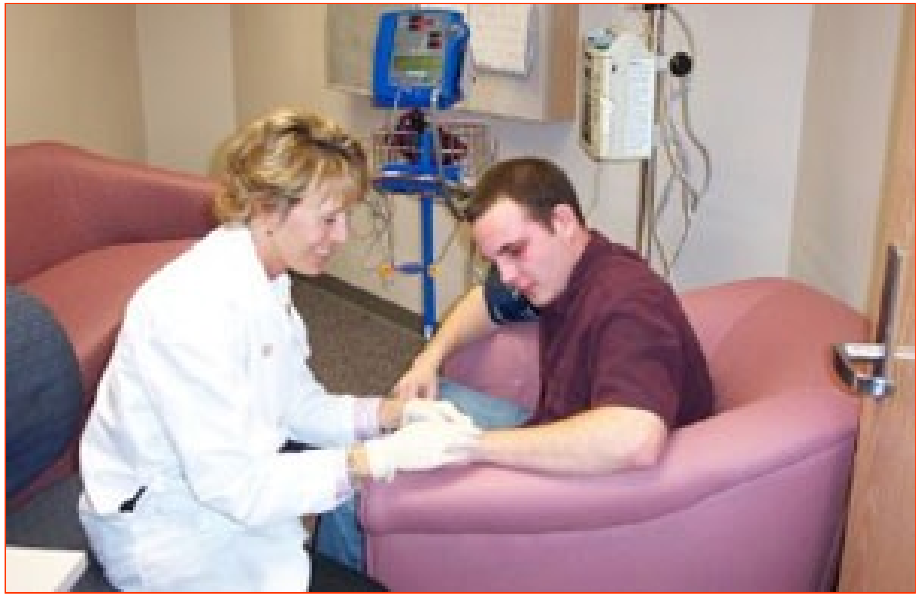
Hemophilia B:

(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

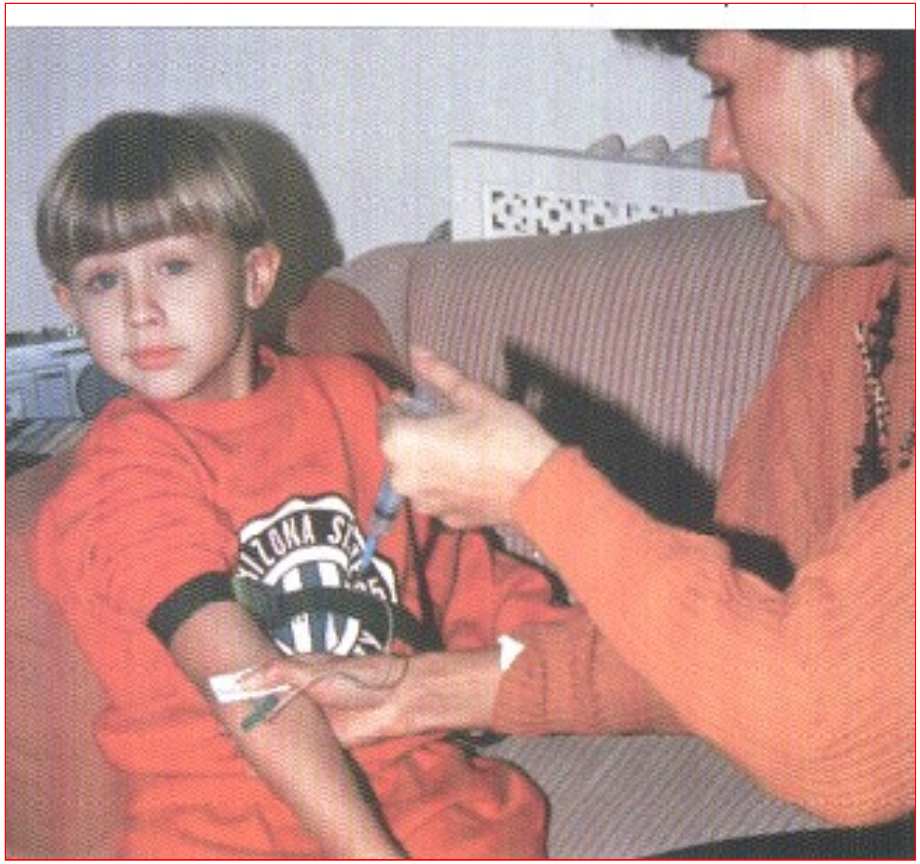
Factor replacement
at the consulting room

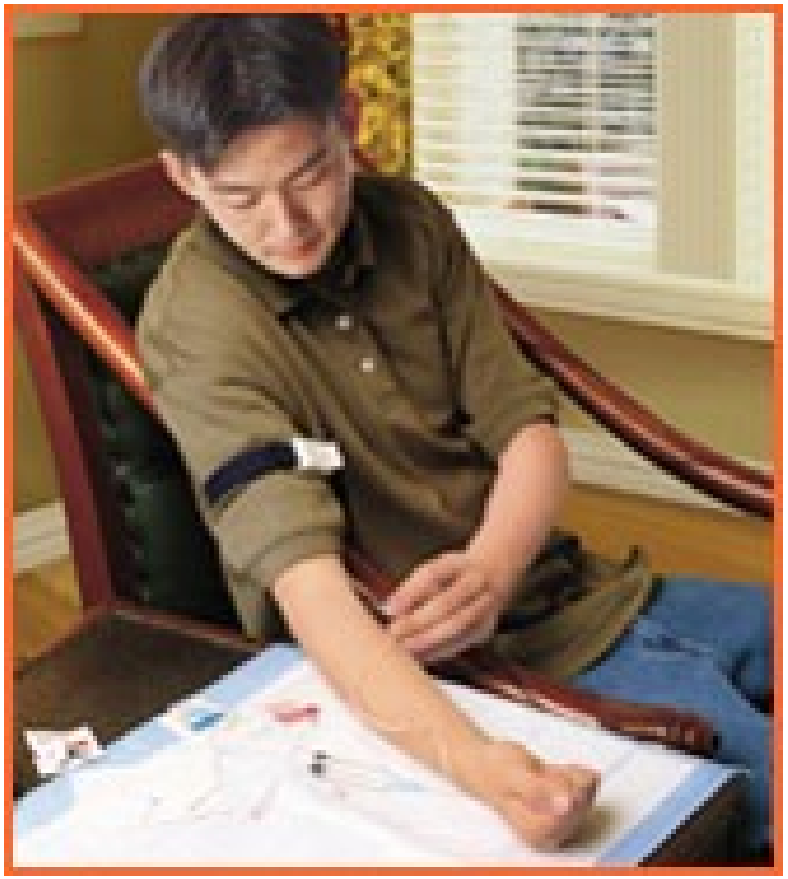


Home therapy:

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

Optimal early treatment.

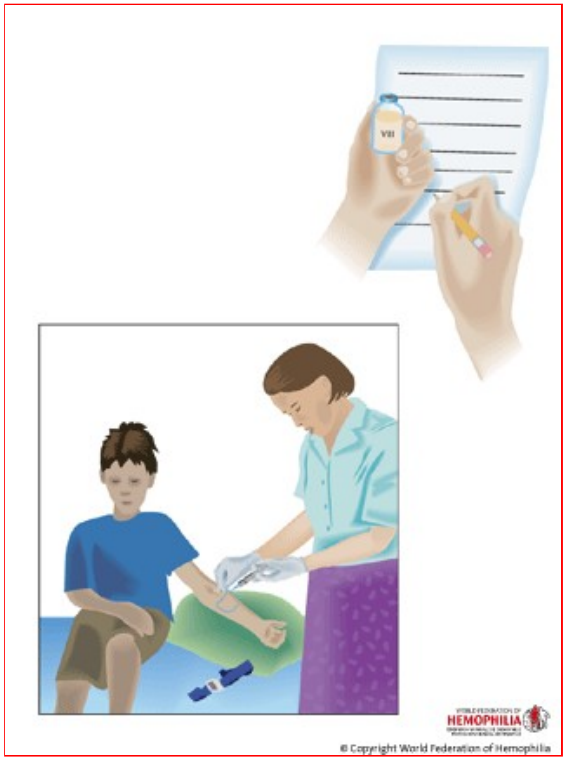




Supplies needed for treatment with factor concentrate:

sharps container
disposable wipes
alcohol wipe
bandage
cotton balls
tape
tourniquet
butterfly needle
syringe
transfer needle/
filter needle
factor concentrate
latex gloves
diluent (sterile water) supplied
with the concentrate

A written record of all treatments must be kept.



Prophylaxis

There is a direct relationship between number of bleeds into a joint and joint damage in *severe hemophiliacs*.

Prophylaxis: ***is the administration of clotting factors at regular intervals to prevent bleeding.***

The aim of prophylaxis:

to maintain the patient's factor VIII/IX level in the „moderate" range (> 1%) to prevent spontaneous joint bleeding.

Forms of prophylaxis:

- **Primary prophylaxis:**

  is initiated before or soon after the first joint bleeding – before the onset of joint damage (usually < 2 years).

- **Secundary prophylaxis:**

  is started after some degree of haemophilic arthropathy has already developed.

- **Tertiary prophylaxis:**

prophylaxis for a specific event

(surgery, postoperative period)

- **Primary prophylaxis:**

  - **Generally recommended *for children* with severe hemophilia**
  - **Initiated after the first episode of bleeding into joints or after other frequent bleedings**
  - **Can usually be discontinued upon depletion of growth phase**
  - **Individual adjustment of the treatment**

Mean dose: **20-30 IU/kg BW 3 times/week (hemophilia A)**

2 times/week (hemophilia B)

Inhibitors:

The major complication of replacement therapy is formation of antibodies *(alloantibodies)*, which *inhibit FVIII/FIX activity,* thus dramatically *reducing treatment efficiency.*

Frequency: - Hemophilia A: 10-15 %
- Hemophilia B: 1-3 %

(FIX inhibitors can be associated with an allergic reaction during FIX administration).

The majority of inhibitors develop within the first 10-20 exposure days.
The amount of antibody can be measured by using *Bethesda inhibitor assay.*

Low titer: < 5 *Bethesda units (BU)*, high titer: > 5 *BU*.

Treatment hemophilia with inhibitor

- **Management of bleeding:**
  - **Low titer inhibitor:**
    - **High dose FVIII/FIX (to neutralize the inhibitor with excess factor activity and stop bleeding)**
  - **High titer inhibitor:**
    - **Bypassing agents:**
      - **Activated prothrombin complex concentrates (APCC):**
        - » **FEIBA (factor eight inhibitor bypass activity): 50-100 U/kg every 6-12-24 hours**
      - **rFVIIa (NovoSeven): 90-100 µg/kg every 2-3 hours**
- **Immune tolerance induction:**
  Prolonged administration of factor to induce immune tolerance
  - **Low titer inhibitor: 50-100 U/kg FVIII/FIX daily**
  - **High titer inhibitor: 150-200 U/kg FVIII/FIX daily**

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.

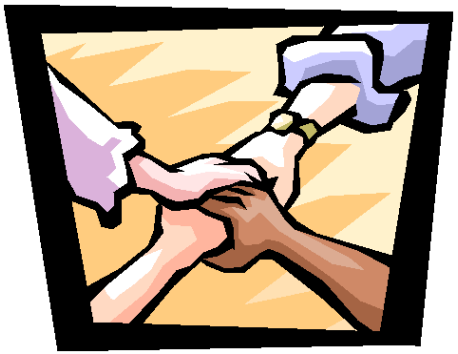
Dental health is very important in hemophilia:

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

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

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

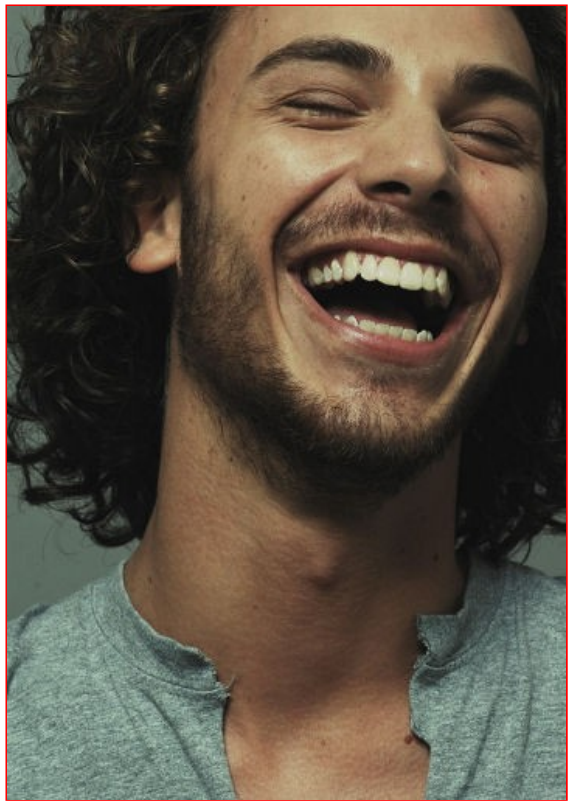
- Cooperation between hematologists (hemostaseologists) and dentists is necessary.



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

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

The life expectancy of someone with hemophilia varies depending on whether they receive proper treatment:

- without adequate treatment, many people with hemophilia die before they reach adulthood.

(Only 25% of hemophiliacs receive proper treatment on the world!)

- with proper treatment, life expectancy for people with hemophilia is about 10 years less than that of males without hemophilia, and *children can look forward to a normal life expectancy*.

- **With modern treatment, children born with hemophilia can expect to live a long, full life.**
- **Prophylaxis improves quality of life.**
- **A new generation of zero joint score adult patients is coming.**