Causes of Excessive Bleeding

- Any clotting factor deficiency
  - Most Commonly :
    - **Hepatocellular disease**
    - **Vitamin K deficiency**
    - **Hemophilia** Deficiency in clotting factor 8.
    - **Low platelet count (thrombocytopenia)**

By Lujain Ahmad.

Vitamin K Deficiency

- essential for the production of prothrombin in the liver.

- **Essential to carboxylate glutamic acid in five important clotting factors:**
  - **prothrombin and factors VII, IX, X, and protein C** * Vit K is co factor in adding 7 carboxyl group 8 10 to glutamic acid, and after adding this group Vit K ⇒
- **In this process vitamin K is oxidized and inactivated** so it is need to be activated again by ...
- **Vitamin K epoxide reductase complex 1 (VKOR c1) reduces vitamin K and reactivates it**

Vitamin K

- **Produced in the intestine by bacteria**
- **Fat-soluble: malabsorption of fats can lead to deficiency**
- **Lack of bile production or delivery can cause fat malabsorption and vitamin K deficiency**
- **In patients with liver or biliary disease, vitamin K can be injected 4-8 hours before surgery**

Hemophilia (bleeding disorder)

—has 2 types:

- **Hemophilia A – Deficiency of factor VIII** (8)
  - **85% of hemophilia cases**
  - **1 / 10,000 males** (more common in male)
- **Hemophilia B – Deficiency of factor IX** (9)
  - **15% of cases**
  - **About 1 / 60,000 males** (more common in male)
- **Both impair Intrinsic Pathway activation**
- **Both genes are on the X chromosome (males only get one copy)**
- **Clinically: Bleeding after minor trauma**

Factor VIII Deficiency

- they work together.
- Factor VIII has a partener…Von willbrand factor
- Deficiency of factor VIII causes hemophilia A
  - → treat bleeding with factor VIII replacement
- Deficiency of Von willbrand factor causes von Willebrand disease (resembles decreased platelet function)

Thrombocytopenia

- when the platelet number lower than normal.

- **Low numbers of platelets**
- **Bleeding from small venules or capillaries**
  - unlike haemophilia ⇒ the bleeding occurs in large vessels
- **Petechaiae, thrombocytopenic purpura**
  - the name of this condition
  - Due to the purple petecchies in the skin
- **Often idiopathic**
- severity depends on no. of platelets.
  - **< 50,000 platelets / µL – usually modest bleeding**
  - **< 10,000 platelets / µL – life-threatening** lethal
- **Treated with platelet infusions**

  → **effective for 1 – 4 days each time**

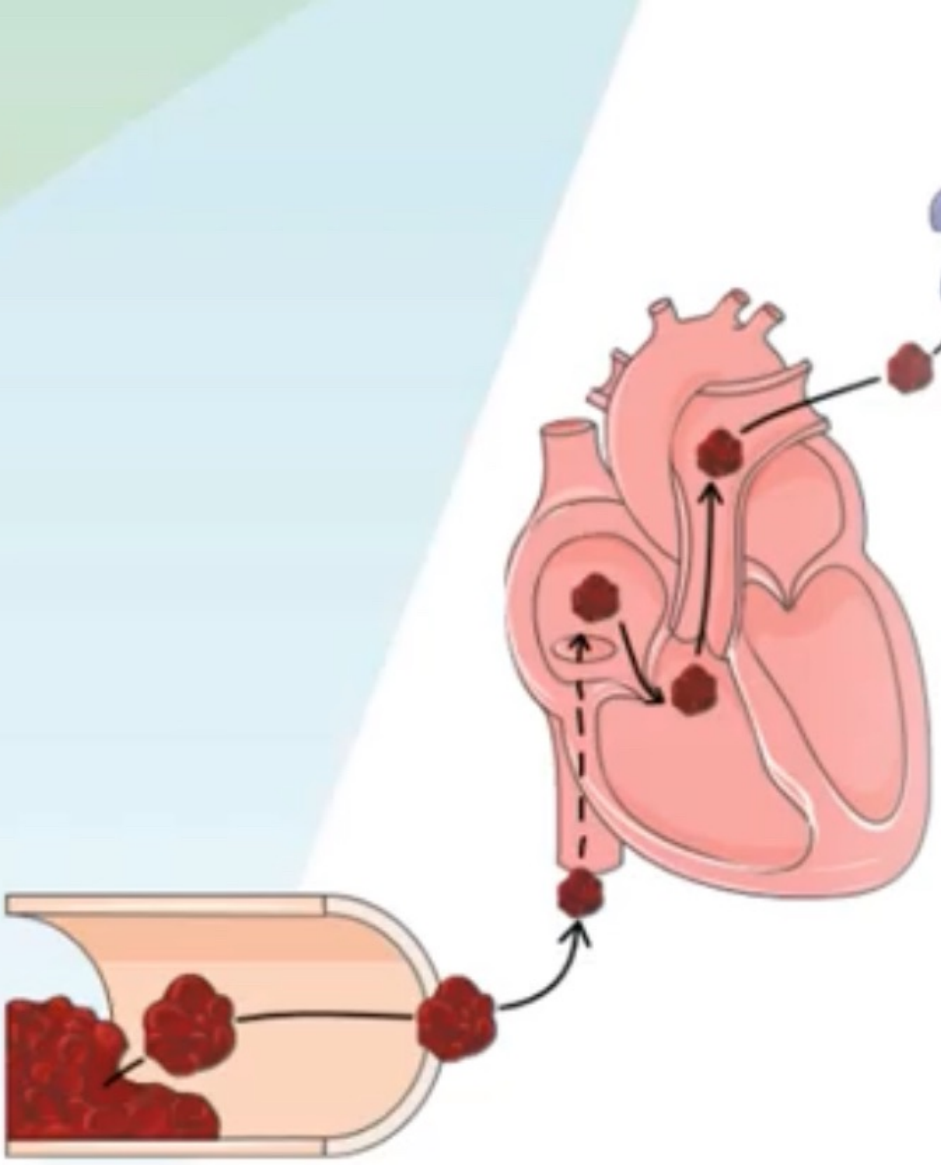
Thrombi and Emboli

- An abnormal clot is a thrombus
- When it floats it's an embolus
- Caused by…
  - Endothelial roughening (e.g. atherosclerosis)
  - Slow flow (e.g. prolonged air travel)
- Treatment…
  - tPA
  - Embolectomy

can be due to

(tissue plasminogen activator factor)

Pulmonary Embolus



- Usually from deep leg veins
- Part of thrombus disengages ~10% of the time
- Occludes pulmonary arteries—potentially fatal
- tPA can be life-saving

So it block the blood supply

Disseminated Intravascular Coagulation (DIC)

(Serious Condition)

- Occurs in the setting of massive tissue damage or sepsis which will result in ∞
- Wide-spread coagulation in small vessels
- Manifested as bleeding from multiple sites because of depletion of clotting factors

causing circulatory shock.

Clinically Useful Anticoagulants

Heparin

- Binds, potentiates antithrombin III
- Works rapidly, generally used acutely

Coumarins an oral medication

- Inhibit VKOR c1 the enzyme that activate Vit. K.
- Deplete active vitamin K → deplete active prothrombin, factors VII, IX, X
- Slower acting (days); used chronically
- Over-anticoagulation – Treat with FFP and vitamin K

Fresh Frozen Plasma

In vitro Anti-coagulation

1. • **Siliconized containers prevent activation of factor VII and platelets**
2. • **Heparin – used in blood collection, heart-lung and kidney machines**
   ↳ and in machines used in blood transfer.
3. • **Calcium chelators (citrate, EDTA) used in blood collection, blood storage**

– Oxalate also can be used but citrate is more safe

Blood Coagulation Tests

① Bleeding

Bleeding Time (from small cut)

- normally 1 - 6 minutes
- Largely reflects platelet function

we make it

If the platelet number or function are deficient it take longer time

② Clotting

Clotting time

- Invert tube every 30 seconds
- Normally 6 – 10 minutes
- Not reproducible, generally not used

It is not used nowadays.

There are high variability in clotting time using different methods.

Bleeding time

- A **bleeding time** is used to evaluate the second phase of hemostasis, which involves adherence of the platelets to the injured vessel, platelet activation and aggregation (formation of a plug).

✓ The time measures how long it takes for a platelet plug to form.

✓ It increases when the platelets count is low (thrombocytopenia), platelet function is abnormal or with the use of aspirin.

- anticoagulant inhibits the production of prostaglandin and TXA_2

- Disadvantages: Insensitive, Invasive & operator dependent.
- Advantages: good test to evaluate the platelet's function and structural abnormalities.

The Duke method

you will learn it in the lab.

1. Clean the tip of the finger or the ear lobe with alcohol.
2. Puncture the skin with a special lancet. The wound should be 3–4 mm deep.
3. Wipe the blood drop by a filter paper every 30 seconds
4. Repeat until no more blood is absorbed by the filter paper. Which indicates a platelet plug has formed
5. Multiply the number of blood drops by 30 seconds
   - Or divide the number of spots of blood by 2 and that will give you the bleeding time in minutes.
   - Normal value: is less than 5 minutes

Clotting time

- It measures the time required for a blood sample to coagulate in vitro. Clotting time depends on the **availability of coagulation factors.**

- Many techniques are used the one we use in our lab depends on using non-hepranized capillary tubes

- Clotting time is prolonged in conditions like hemophilia, vitamin K deficiency, liver diseases, and warfarin overdose.

anticoagulant treatment.

Prothrombin Time

- It is measured by ...

- **Add excess calcium and tissue factor to oxylated blood, measure time to clot**

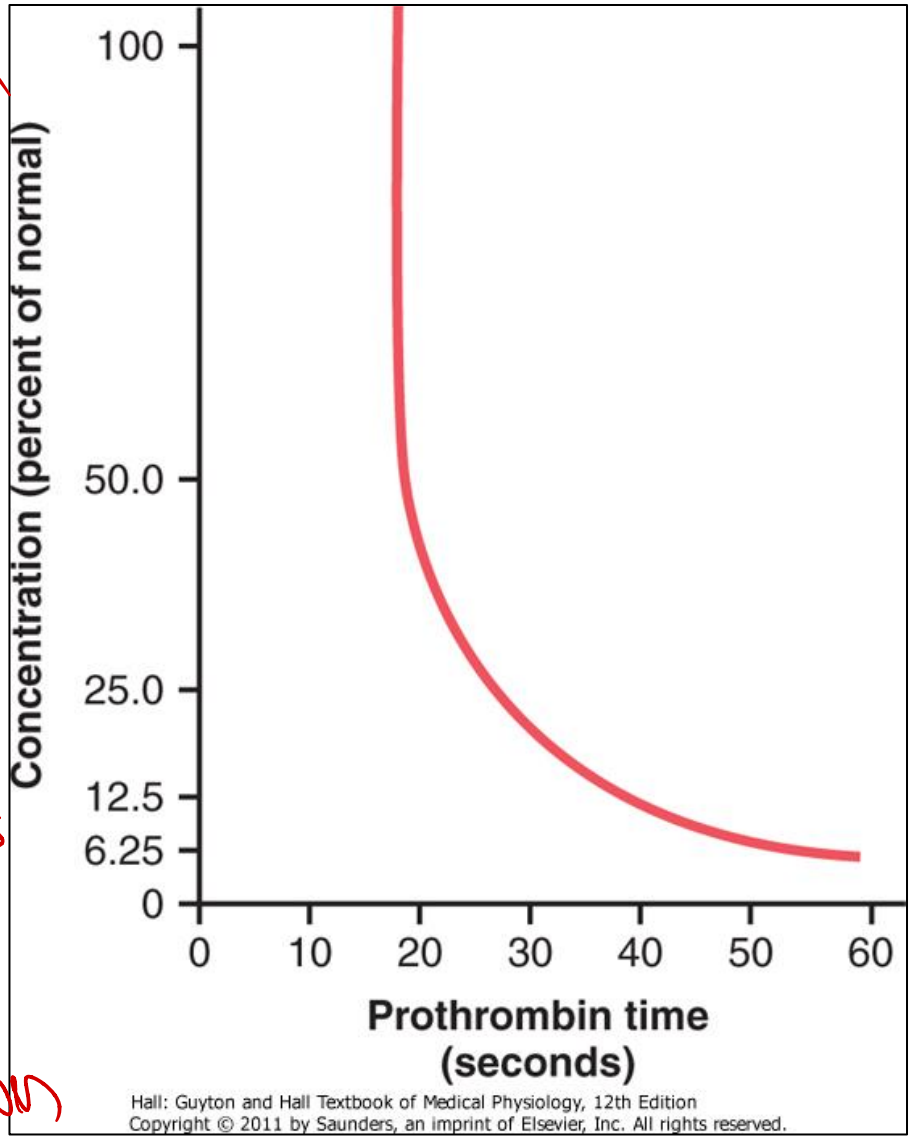
- **Assesses Extrinsic and Common Pathways**

- **Usually about 12 seconds** (in normal state)
- If that was prolonged, then there is a problem in PT.
- **Tissue factor batches have to be standardized (activity expressed as "International Sensitivity Index (ISI)")**

↳ which accounts for the sensitivity of the TF that was used for the measurement of prothrombin time

Prothrombin Concentration and Function

- Prothrombin time correlate with the conc. which is a percentage of normal, so if we measure prothrombin time in seconds we can detect the estimation of concentration



→ used before surgery.

International Normalized Ratio (INR)

- standrized ISI which depends on the sensitivity of TF that was been used.

$$INR = \left(\frac{PT_{test}}{PT_{normal}} \right)^{ISI}$$

⟹ $\frac{\text{The patient prothrombin time}}{\text{normal prothrombin time}}$

- If it less than that, there is a tendency for clotting

- **Normal INR: 0.9 – 1.3**
- **Therapeutic range: 2.0 - 3.0**

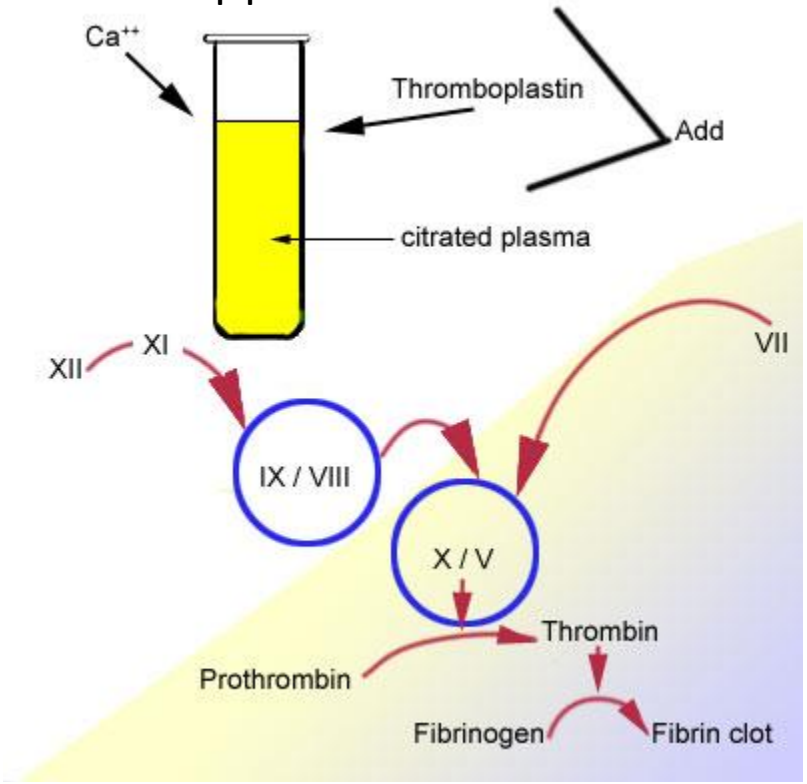
If it more than that, it reflects the tendency for bleeding

Tests of Other Clotting Factors

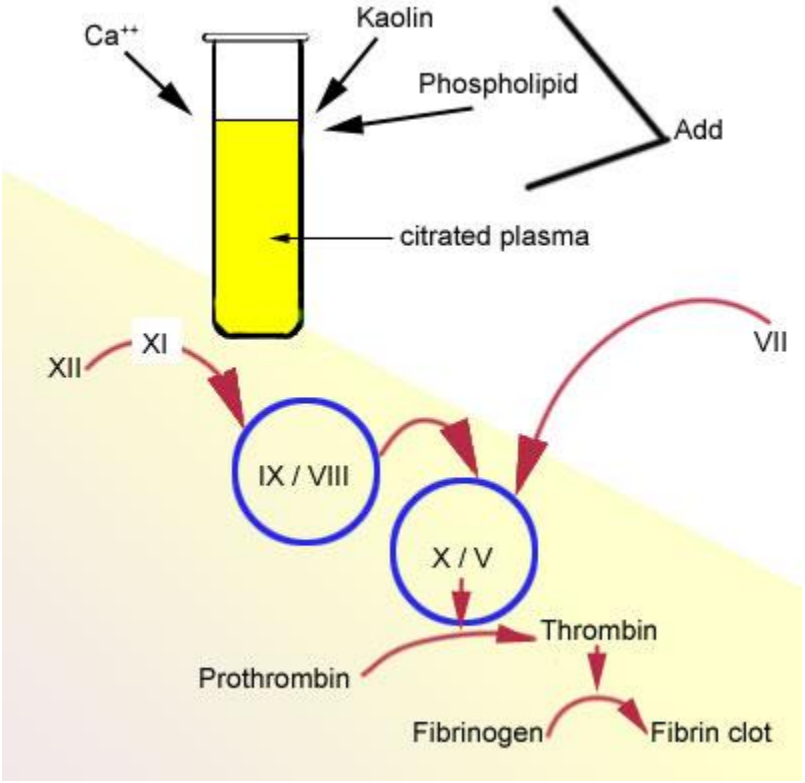
- **Mix the patient's plasma with a large excess of all needed components except the factor being tested**, If the time of clotting was higher than normal, then there's a deficiency in that factor.
- **Compare time to coagulation with that for pooled plasma of healthy volunteers**

-Doctor Shop here.

PT


Ca++
Thromboplastin
Add
citrated plasma
XII
XI
VII
IX / VIII
X / V
Thrombin
Prothrombin
Fibrinogen
Fibrin clot

aPT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aPTT

- The activated partial thromboplastin time (aPTT) is a test performed to investigate bleeding disorders and to monitor patients taking an anticlotting drug such as heparin which inhibits factors X and thrombin, while activating anti-thrombin.

The aPTT test uses blood which is decalcified to prevent clotting before the test begins. The plasma is separated by centrifugation. (Ionized) Calcium and activating substances are added to the plasma to start the intrinsic pathway of the coagulation cascade. The substances are: kaolin (hydrated aluminum silicate) and cephalin. Kaolin serves to activate the contact-dependent Factor XII, and cephalin substitutes for platelet phospholipids.

- The partial thromboplastin time is the time it takes for a clot to form, measured in seconds. Normally, the sample will clot in 35 seconds.

PTT measures the integrity of the intrinsic system (Factors XII, XI, VIII, IX) and common clotting pathways.

Increased levels in a person with a bleeding disorder indicate a clotting factor may be missing or defective. At this point, further investigation is needed and warrants the use of sensitive assays for specific coagulation factors. Liver disease decreases production of factors, increasing the PTT.