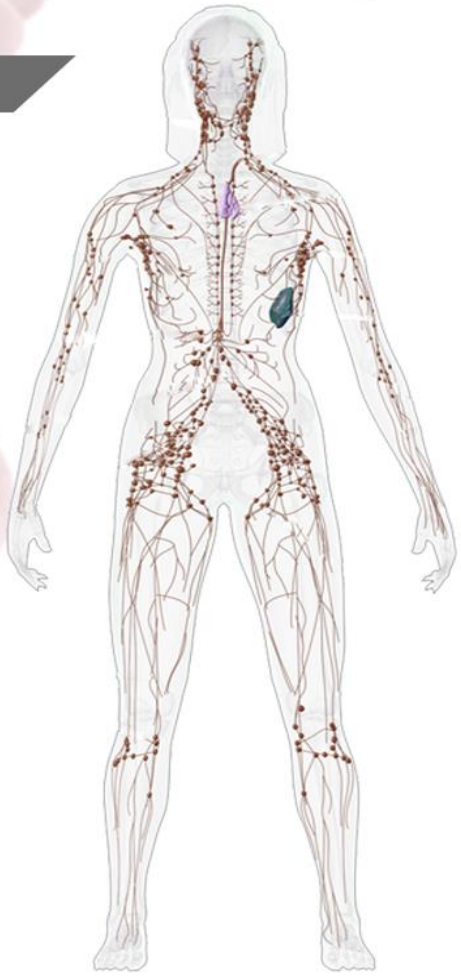
Sheet 10

# Hematology and Lymphatic system

Subject | Pathology

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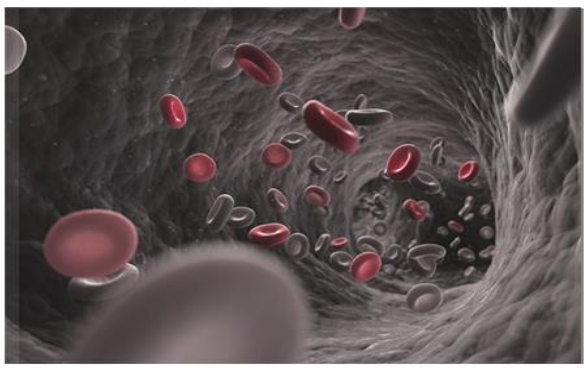


# Bleeding disorders

When bleeding occurs, 3 mechanisms work together to contain the bleeding. The first stage is at the level of blood vessel; contraction and constriction occurs to limit the amount of blood loss because of the injury. And then, primary hemostasis which is related to platelets. Platelets will be recruited and cause aggregation and temporary clotting or closing of the blood vessel. This clot is not stable and needs to be stabilized, this is when secondary hemostasis (caused by clotting factors) happens to form fibrin at the end of the hemostatic activity.

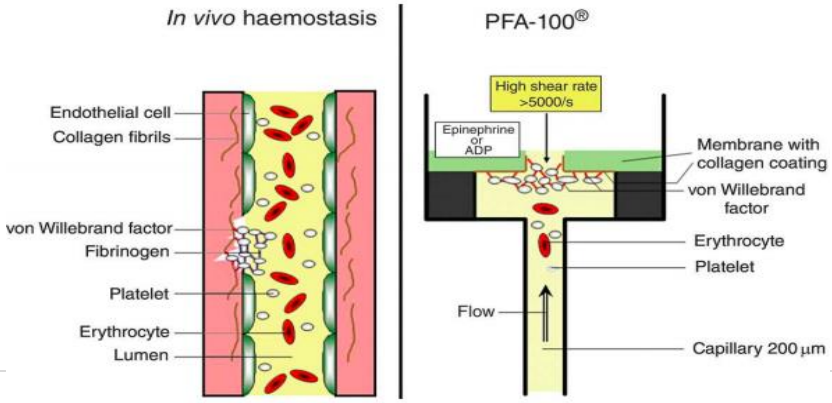
Bleeding disorders are divided into:

- Diseases of the blood vessels
- Platelets disorders
  a. Thrombocytopenia
  b. Functional disorders
- Clotting factors deficiency

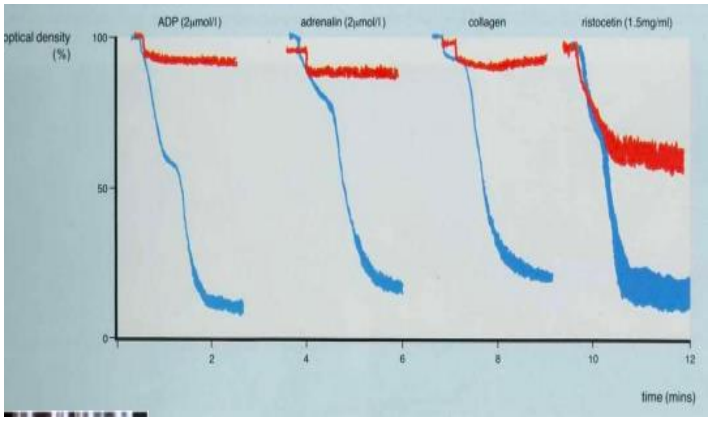
Lab test

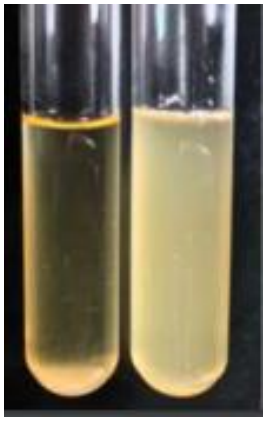
Assessment of bleeding tendency is very important for in patients who are undergoing surgey. *These lab tests are performed daily in labs.*

1- Platelet count (150000-450000): part of CBC panel, the reference range may differ from lab to lab. Does not mean bleeding will occur if slightly decreased.
2- Tests that assess platelet function:
   - Bleeding time: old and outdated; it doesn't correlate with the risk of surgery meaning that a normal BT doesn't necessarily mean that the patient won't bleed and vice versa.
   - Platelet Function Assay: modern test. The left side of the picture is a schematic representation of the blood vessel. The PFA tries to imitate this. it is composed of a chamber and a small narrow tube. The blood will go in high velocity and will encounter certain platelet adhesion and aggregation agonists (e.g. ADP, collagen, epinephrine). The closure time is calculated (the time that this aperture takes to close completely), this reflect the functionality and the no. of platelets, meaning their ability to close that aperture.



- Aggregation studies: looks at the surface mlcs of platelets; receptors that are involved directly in platelet aggregation and adhesion. The principle of this test is fairly simple, we take a tube filled with platelet-rich serum (no RBCs) and add agonists to it (i.e. ADP, collagen, epinephrine, and ristocetin). Platelet aggregation studies are most commonly abnormal in patients who receive medication (e.g. aspirin, clopidogrel which is an ADP antagonist).
  *<u>Left tube:</u> Normally functioning platelets will aggregate in response to these agonists and move to the bottom of the tube increasing the optical density (more transparent). <u>Right tube</u>: if the platelets fail to aggregate, that implies a functional dysfunction in the platelets and the density stays the same. The density is reflected on the graph by the blue line indicating normal platelets and the red line indicating abnormal platelets. Notice that the optical density of the red line stayed the same in spite of adding agonists, this implies a functional problem in platelets in which they can't respond to ADP, collagen, epinephrine. <u>Ristocetin</u> has a partial response: the dysfunction related to it is partial not complete*. *You don't need to know the interpretation of this picture nor what ristocetin is, this is just an example to elaborate on the concept.*



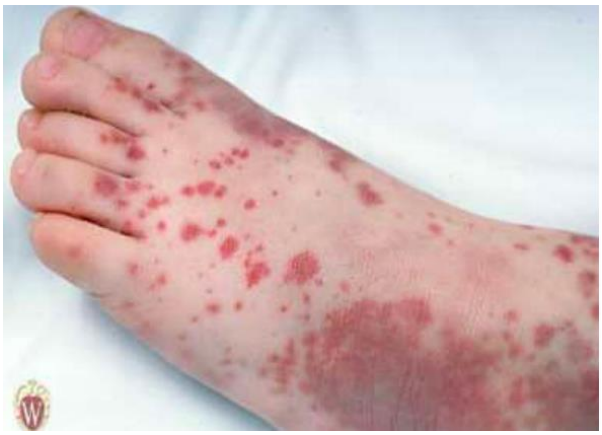



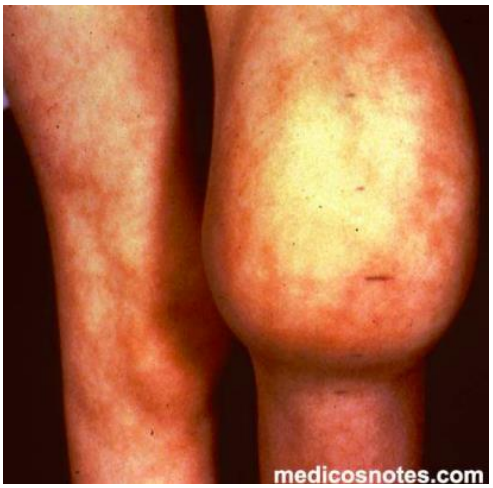
- PT: prothrombin time: Extrinsic and common pathways
- PTT: Partial thromboplastin time: intrinsic and common pathways
- D dimer and fibrin split products: Sensitive for DIC but not specific; if we suspect DIC but the D dimer and fibrin split products are negative then the patient definitely doesn't have DIC. Their positivity doesn't necessarily mean there is DIC.

<u>Two major clinical types of bleeding:</u>

- **Mucocutaneous:** seen in <u>disorders of the vessels and platelets</u>. Presents as petechiae and ecchymosis. Picture: large ecchymosis on lateral side of foot, small petechiae.

❖ **Deep bleeding** in muscles and large joints seen in clotting factor deficiency. Picture: bleeding in knee joint is a common presentation especially in hemophilia.






# Disorders related to blood vessels

Blood vessels play an important role in the very beginning of hemostasis to control bleeding.

1- **Increased vascular fragility:** Normal platelet count, function, PT and PTT; because platelets and clotting factors are normal. Caused by:
   - Vitamin C deficiency (scurvy)
   - Amyloidosis (deposition of abnormal proteins in the blood vessel wall)
   - Chronic steroid use
   - Vasculitis (inflammation of vessels)

2- **Endothelial damage:** tends to be more serious. Caused by:

   - **DIC:** the prime example of endoth. damage. Overwhelming damage to the endothelial cells resulting in exposure of the underlying tissue that is highly prothrombotic (converting them to prothrombotic surfaces). The thrombosis is widespread in the vasculature with subsequent consumption of platelets and coagulation factors (consumptive coagulopathy)
     It occurs as a complication of a wide variety of disorders; it is caused by the systemic activation of coagulation and results in the formation of thrombi throughout the microcirculation, consumption of platelets and coagulation factors and severe bleeding. *So, widespread enoth. damage → widespread thrombosis.*
     Causes of endothelial damage:
       1- Obstetric complication, placental damage

       2- Cancer: Acute Promyelocytic Leukemia and adenocarcinomas (specifically *pancreatic adenocarcinoma*).
       Mechanism: release proteolytic enzymes and tissue factor

3- Overwhelming bacterial sepsis
Mechanism: Endotoxins trigger release of tissue factors from monocytes. Monocytes also release IL1 and tumor necrosis factors; both increase tissue factor and decrease thrombomodulin

4- Deposition of antigen-antibody complex such as in SLE: the complex cause activation of thrombosis

5- Extremes of temperature

6- Major trauma; specifically major skeletal muscle traumas and severe head trauma

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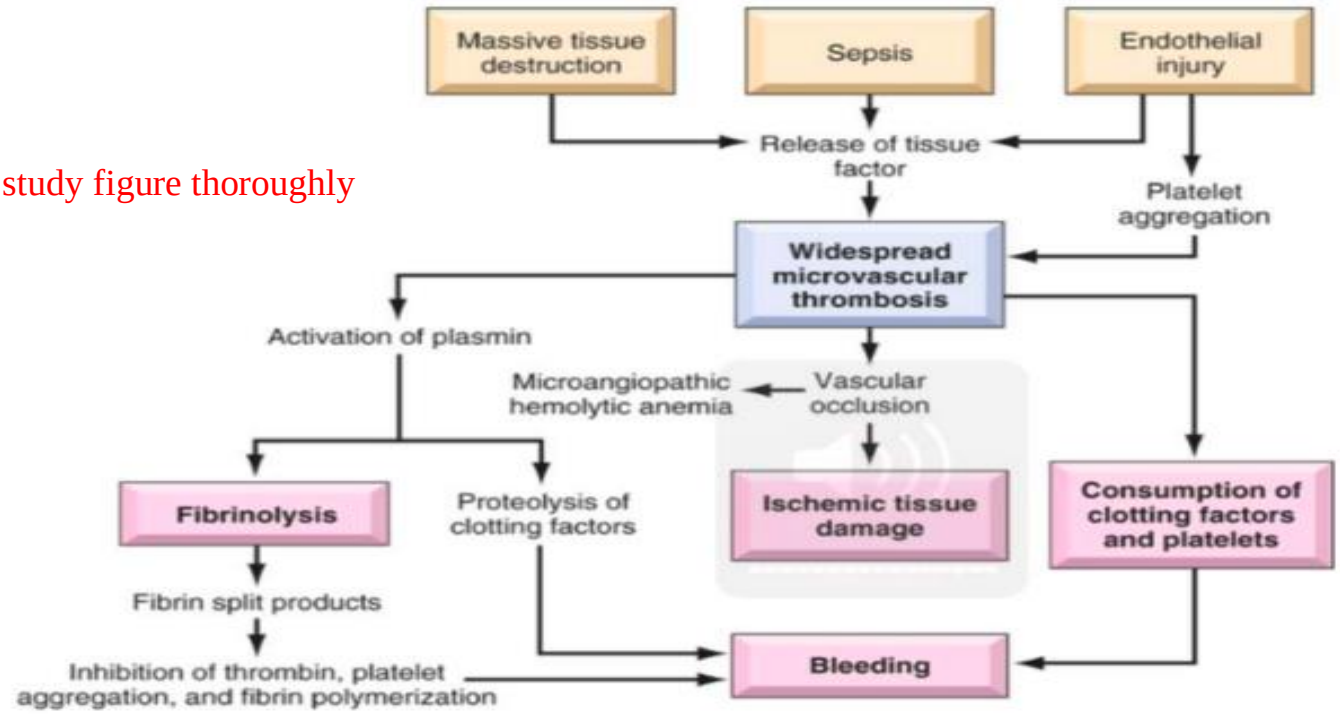
| **Obstetric Complications** |
| Abruptio placentae |
| Retained dead fetus |
| Septic abortion |
| Amniotic fluid embolism |
| Toxemia |
| **Infections** |
| Sepsis (gram-negative and gram-positive) |
| Meningococcemia |
| Rocky Mountain spotted fever |
| Histoplasmosis |
| Aspergillosis |
| Malaria |
| **Neoplasms** |
| Carcinomas of pancreas, prostate, lung, and stomach |
| Acute promyelocytic leukemia |
| **Massive Tissue Injury** |
| Trauma |
| Burns |
| Extensive surgery |
| **Miscellaneous** |
| Acute intravascular hemolysis, snakebite, giant hemangioma, shock, heat stroke, vasculitis, aortic aneurysm, liver disease |

This table shows causes of DIC.
I marked the points the Dr read.

study figure thoroughly

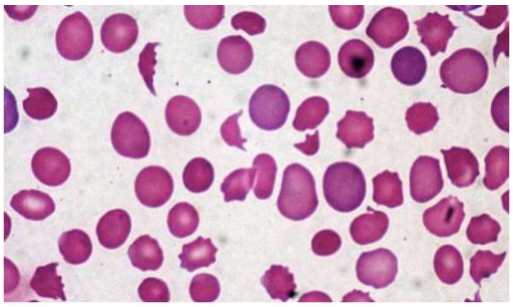


Notes:

- Wide spread microvascular thrombosis leads to vascular occlusion. As we know, obstruction of blood vessel by fibrin strands will result in MAHA by directly rupturing RBCs, and the image will show schistocytes.
- DIC is basically a systemic disease consisting of combination of bleeding and coagulation (coagulation→ consumption of factors/platelets→ bleeding)
- Wide spread microvascular thrombosis will also activate plasmin which will cause proteolysis of clotting factors further aggravating the bleeding tendency.
- Plasmin will also cause fibrinolysis and increase in fibrin split products. That is why we always see in DIC high fibrin split products and that iss whyyy when the assay for fibrin split products is negative, the patient is really unlikely to have DIC (sensitive markers).

Morphology:

- Intravascular hemolysis with schistocytes (as in any cause of MAHA). *Schistocytes are the hallmark of intravascular hemolysis.*
- Microthrombi in the small vessels and capillaries of various organs.



Clinical manifestations:

- Variable
- Could be acute (as in postpartum DIC) or chronic (as in cancer)
- Can be minimal or
- severe resulting in: widespread ischemia, shock, acute renal failure, dyspnea, cyanosis, convulsions, coma and death.

Lab findings:

- Low platelets: due to consumption
- High PT and PTT: due to consumption of clotting factors
- Elevated FDPs

Treatment:

- Depends on clinical presentation
  Mainly bleeding → replacement of coagulation factors
  Mainly thrombosis → heparin

Prognosis:

- depends on the severity of presentation and the underlying condition.

# Platelet disorders: Thrombocytopenia

- Low platelet count: Less than 15000
  It's unlikely that bleeding happens upon mild depression of platelet count. Bleeding typically starts to occur when below 20000.
- 20000-50000 → patient suffers from post-traumatic bleeding
  Less than 5000 → spontaneous bleeding especially intracranial and that is why it should be treated immediately.

- YOU SHOULD NOT TREAT MILD THROMBOCYTOPENIA; a patients who has no bleeding and presents with 150000 count should not be given platelets nor treated.

- Platelet-caused-bleeding tend to be Mucocutaneous with mucus surfaces and skin hemorrhages such as ecchymosis and petechiae. Brain hemorrhage is a major factor for mortality

**Causes of thrombocytopenia:**

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| **Decreased Production of Platelets** |
| **Generalized Bone Marrow Dysfunction** |
| Aplastic anemia: congenital and acquired<br>Marrow infiltration: leukemia, disseminated cancer |
| **Selective Impairment of Platelet Production** |
| Drug-induced: alcohol, thiazides, cytotoxic drugs<br>Infections: measles, HIV infection |
| **Ineffective Megakaryopoiesis** |
| Megaloblastic anemia<br>Paroxysmal nocturnal hemoglobinuria |
| **Decreased Platelet Survival** |
| **Immunologic Destruction** |
| Autoimmune: ITP, systemic lupus erythematosus<br>Isoimmune: posttransfusion and neonatal<br>Drug-associated: quinidine, heparin, sulfa compounds<br>Infections: infectious mononucleosis, HIV infection, cytomegalovirus infection |
| **Nonimmunologic Destruction** |
| Disseminated intravascular coagulation<br>TTP<br>Giant hemangiomas<br>Microangiopathic hemolytic anemias |
| **Sequestration** |
| Hypersplenism may caused by liver cirrhosis |
| **Dilutional** |
| Multiple transfusions (e.g., for massive blood loss) |

- **ITP (**Immune thrombocytopenic purpura):
  Acute: children after a viral infection, self-limiting and doesn't cause long-term consequences.
  Chronic: affects women 20-40 years of age

  Pathogenesis:
  - Antibodies against platelet antigens (IIb/IIIa and IB/IX). The platelets will be covered in antibodies and similar to what happens in immune hemolytic anemia, the spleen will cause damage to these antibody coated platelets.

  Clinical presentation:
  - Mucocutaneous bleeding, and if the depression in platelet count is severe, then brain hemorrhage might be an issue (rare)

  Lab findings:
  - Low platelets
  - Normal PT and PTT: since clotting factors are not affected
  - Bone marrow shows megakaryocytic hyperplasia *(similar to the concept of erythroid hyperplasia seen in immune hemolytic anemia )*: rarely done as the diagnosis is usually straight forward.

  Treatment:
  Acute → self-limited. However, steroids are required (immunosuppressive therapy).
  Chronic → splenectomy to overcome the deleterious effect of spleen on ab-coated platelets.

- **HIT (**heparin induced thrombocytopenia):
  Occurs in 3-5% of patients using unfractionated heparin *(IV)*. Heparin is used to treat certain thrombotic disease.
  - Develops after 1-2 weeks after initiation of therapy.
  - Results in thrombosis associated with low platelets.
  - Use of low molecular weight heparin is advocated as it has low risk of HIT but NOT ZERO!!

  Pathogenesis:
  - IgG antibodies against platelet factor 4 (PF4) are the culprits.

  Treatment:
  - HIT is a severe disease and is best treated with **cessation of heparin** and use of LMWH

Clinical presentation:

- The classical presentation for HIT is a young patient receiving heparin for DVT who suffered from lower limb ischemia due to thrombosis after one week of initiation of therapy. The ischemia could be sever enough to result in amputation.

- **TTP and HUS:** Both have widespread microthrombi

**TTP (thrombotic thrombocytopenic purpura):**
PENTAD OF FINDINGS:
1- Fever
2- Thrombocytopenia
3- Microangiopathic hemolytic anemia
4- Neurological manifestations
5- Renal failure

**HUS (and hemolytic uremic syndrome):**
Frequently in children secondary to E. coli infection
1- Fever
2- Thrombocytopenia
3- Renal failure
4- NO neurologic manifestations

So how are they different from DIC???
No significant consumption of clotting factors = Normal PT and PTT
However, platelets will be consumed and thrombocytopenia is present in both of these diseases.

# Coagulation disorders

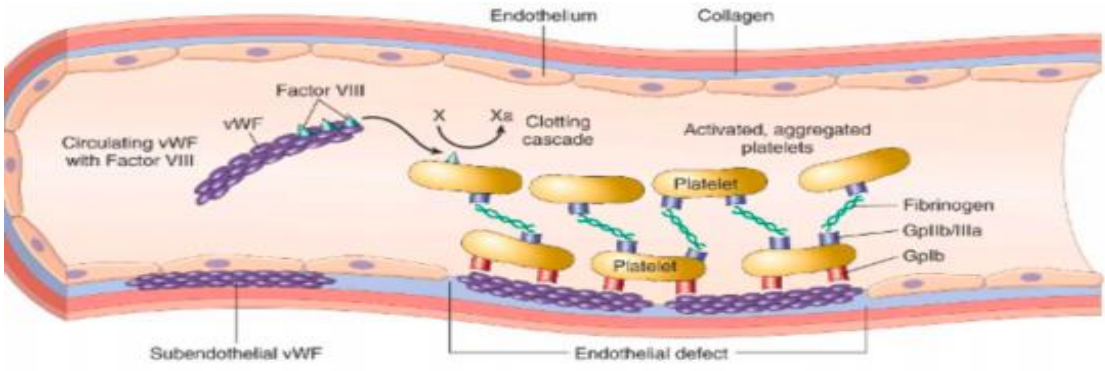
- *Hereditary or acquired*
- *Acquired is more common*
  - ***Vitamin K deficiency*** → *deficiency of factors II, VII, IX, and X*
    - *affects newborns because they don't have enough vit K, and that is why "vit K injection" is given TO ALL CHILDREN immediately after birth*
    - *Patients with fat malabsorption (e.g. cystic fibrosis) since vit K is fat soluble (ADEK)*
  - ***Liver disease*** → *liver is source of most clotting factors*
  - ***DIC*** → *consumption of factors*

- *Hereditary*
  - ***Von-Willebrand disease***
  - ***Hemophilia A***
  - ***Hemophilia B***

  - **Von-Willebrand disease:** *The most common inherited bleeding disorder*
    Functions of vWF: normally present under the endothelium. Endothelium exposed; then vWF attracts platelets which have receptor for this factor. The other function is that it carries factor VIII *(imp in intrinsic pathway)* in the blood.
    - Autosomal dominant
    - 1% of the US population
    - Frequently asymptomatic and under recognized bcz deficiency tends to be mild.

    Pathogenesis:
    - Results in inability of platelets to adhere to sight of injury. Also results in factor VIII deficiency. However, the bleeding is mucocutaneous NOT DEEP bleeding in spite of factor VIII deficiency.
    - Mucocutaneous bleeding: skin petechiae or mucousal bleeding.

    Lab findings:
    - Normal platelet count: functional issue not a count issue
    - Abnormal platelet aggregation studies: bcz vWF which typically adheres to one of the receptors is abnormal
    - Elevated PTT: due to factor VIII deficiency.
    - Normal PT



- **Hemophilia A**

  Deficiency in factor VIII

  X-linked disorder, affects chiefly males

  Most cases are associated with low factor VIII level: 10% are associated with normal level of factor VIII but reduced activity. *So,* most cases related to deficiency

  - Deep muscle and joint hemorrhage (hemarthrosis)

  Lab findings:
  - Normal platelet count and function
  - Normal PT
  - Elevated PTT that corrects with mixing studies

    *mixing studies: we take the patient's serum, we examine clotting factor VIII, then we add normal serum with sufficient amount of factor VIII. And then the PTT will go back to normal*

- **Hemophilia B**: "Christmas disease": *It is less common than hemophilia A*

  Factor IX deficiency

  X-linked disorder, affects chiefly males

  - Deep muscle and joint bleeding (hemarthrosis)

  Lab findings:
  - Normal platelet count and function
  - Normal PT
  - Elevated PTT that corrects with mixing studies

    *Same as hemophilia A*

How to distinguish bw Hemophilia A/B??

Distinguish by doing specific assays that measure the actual levels of factors VIII, and IX