((Primary Homeostasis & related bleeding disorders))

- There are two stages of homeostasis:
  - → Primary: formation of a weak platelet plug
  - → Secondary: stabilizing the platelet plug via fibrin resulting from coagulation cascade
- Primary homeostasis:
  1. Transient vasoconstriction of the damaged vessel
  2. vWF will bind to the damaged area and act as a liker molecule to facilitate binding of platelets to it through (GpIb)
  3. ADP & thromboxane-A_2 will be released from platelets ⟶ leading to expression of GpIIb/GpIIIa on surface of platelets (for platelet aggregation via Fibrinogen)
- Disorders of primary homeostasis:
  - → Due to abnormalities in platelets
    - → Quantitative
    - → Qualitative
  - → Clinical features:
    - * → Mucosal bleeding: epistaxis, hemoptysis--etc
    - → Skin bleeding: petechiae, purpura, ecchymoses easy bruising
  - → Useful laboratory studies include:
    - → Platelet count: normally 150,000 - 400,000/μL
    - → Bleeding time: normally 2-7 minutes
    - → Blood smear
    - → Bone marrow biopsy: maybe there are no megakaryocytes ☹

* vWF: comes from α-granules of platelets & from endothelial cells
  ⇓
  Notice that in endothelial cells, vWF is stored in "Weibel-palade bodies"
* ADP: is stored in dense granules in platelets
* Thromboxan-A_2 is a derivative of platelet cyclooxygenase pathway

* Notice that intracranial bleeding occurs with severe thrombocytopenia
* Purpura > 3mm
* Ecchymoses > 1 cm

1 ITP (Immune Thrombocytopenic Purpura):

- → Autoimmune disease with production of IgG against platelet antigens (GpIIb/IIIa) ⟹ These antibodies are produced by plasma cells in the spleen
- → Splenic macrophages will eat platelets bound to antibodies
- → Acute form (arising in children):
  - → Thrombocytopenia weeks after viral infection or immunization ⟶ This is self-limited
- → Chronic form (arising in adults):
  - → In women of childbearing age
  - → Can be:
    - → Primary: idiopathic
    - → Secondary: e.g. SLE

1] ITP (continued):
- Chronic form (continued):
  - Anti-platelet IgG can cross the placenta resulting in short-lived thrombocytopenia in offsprin.
- Laboratory findings:
  - ↓ platelet count
  - Normal PT/PTT (coagulation cascade is normal)
  - ↑ megakaryocytes on bone marrow biopsy
- Treatment:
  - Corticosteroids: children respond well but adults relapse
  - IV immunoglobulin: effect is short-lived
  - Splenectomy: Therefore eliminating the source of antibodies and site of destruction

2] Microangiopathic hemolytic anemia:
- A platelet microthrombus is formed in small blood vessel → RBCs pass → they are sheared → resulting in schistocytes
- As microthrombi are formed, platelets are consumed
- This condition is seen in:
  - Thrombotic Thrombocytopenic Purpura (TTP): microthrombi are formed due to deficiency is ADAMSTS13 either due to a genetic defect or production of autoantibody against it
  - Hemolytic Uremic Syndrome (HUS): platelet microthrombi are formed due to infection with E. coli O157H7 especially in kidneys
  - Clinical findings of TTP & HUS
    - Skin & mucosal bleeding (↓ platelets)
    - Microangiopathic hemolytic anemia
    - Fever
    - Renal insufficiency (↑ in HUS)
    - CNS abnormalities (↑ in TTP)
  - Laboratory findings:
    - Thrombocytopenia & ↑ bleeding time
    - Normal PT/PTT (coagulation is normal)
    - Anemia with schistocytes
    - ↑ megakaryocytes on bone marrow biopsy

* ADAMSTS13: converting multimers of vWF into small monomers (which can be used).
* E. coli O157H7 is especially seen in children who get exposed to undercooked beef
* Treatment of TTP:
  - Plasmapheresis
  - Corticosteroids

((Primary Homeostasis & Related Bleeding Disorders))

[3] Bernard-Soulier Syndrome:
- → Genetic (GpIb) deficiency thus platelet adhesion cannot occur
- → Blood smear shows mild thrombocytopenia with enlarged platelets

[4] Glanzmann thrombasthenia:
- → Genetic (GpIIb/IIIa) deficiency thus platelet aggregation is impaired

[5] Aspirin:
- → It irreversibly inactivates cyclooxygenase thus thromboxane-A2 will not be formed

} These are qualitative disorders of platelets

((Secondary Homeostasis & Related Disorders))

* Review coagulation cascade from physiology

- End product of coagulation cascade is thrombin which will convert fibrinogen into fibrin → that will stabilize the platelet plug
- Coagulation factors are produced in their inactive state from the liver. Activation requires:
  - → Exposure to an activating substance
  - → Phospholipid surface → provided by platelets
  - → Calcium → derived from dense granules of platelets
- Disorders of secondary homeostasis are generally due to factor abnormalities
- Clinical features:
  - → Deep tissue bleeding: muscles and joints
  - → RBbleeding after surgical procedures
- Laboratory studies:
  - → PT: measuring extrinsic and common pathways → measuring warfarin effect
  - → PTT: measuring intrinsic and common pathways → measuring heparin effect

[1] Hemophilia-A:
- → Genetic deficiency of factor VIII
- → X-linked recessive affecting males
- → Presentation: deep tissue, joint and postsurgical bleeding
- → Laboratory findings:
  - → ↑ PTT, normal PT
  - → ↓ factor VIII
  - → Normal platelet count & bleeding time
- → Treatment: recombinant factor VIII

2] Hemophilia - B (Christmas disease):
- → Genetic deficiency of factor IX
- → Clinically resembling hemophilia A

4] Coagulation factor inhibitor:
- → Antibody against a coagulation factor leading to its impairment (anti factor VIII is common)
- → How to differentiate it from hemophilia A?
  - → Mixing study: taking a normal plasma & mixing it with patient's plasma:
    - → PTT corrected : hemophilia A
    - → PTT not corrected : antibody against factor VIII

5] Von Willebrand disease:
- → Autosomal dominant with ↓ levels of vWF thus resulting in problem with platelet adhesion.
  - → Explaining the mild mucosal and skin bleeding which can be seen (primary homeostasis is affected).
- → Laboratory findings:
  - → ↑ bleeding time
  - → ↑ PTT (factor VIII is not stabilized), normal PT
  - * → Abnormal ristocetin test
- → Treatment: desmopressin (which will increase release of vWF from Weibel-Palade bodies of endothelial cells).

* Ristocetin: normally causes platelets to aggregate. With lack of vWF → there will be no aggregation

6] Vitamin K deficiency:
- → Vitamin K is important for production of following factors: II, VII, IX, X, C and S
- → vitamin K is activated by epoxide reductase in the liver
- → vitamin K deficiency occurs in:
  - → Newborns: gut is not yet colonized by bacteria
  - → Long-term antibiotic therapy: killing gut flora.
  - → Malabsorption of fat-soluble vitamins (A, D, K and E)
  - → liver failure (measured by PT)

((Other Disorders of Homeostasis))

1. Heparin-induced thrombocytopenia (HIT):
   - Heparin forming a complex with a surface molecule on platelets (heparin-PF4) → IgG will develop against this complex → resulting in destruction of these platelets by the spleen

2. Disseminated Intravascular Coagulation (DIC):
   - There is pathologic activation of coagulation cascade → resulting in many microthrombi which will block blood vessels → ischemia & infarction. Notice that there will be consumption of platelets & factors → resulting in bleeding from IV sites & mucosal surfaces
   - Always secondary to other diseases:
     - Obstetric complication
     - Sepsis: due to endotoxins
     - Adenocarcinoma
     - Acute promyelocytic anemia
     - Rattlesnake bite
   - Laboratory findings:
     - ↓ platelet count (consumed)
     - ↑ PT / PTT
     - ↓ Fibrinogen (consumed in formation of thrombi)
     - Microangiopathic hemolytic anemia
     - D-dimers
   - Treatment: addressing the underlying cause with transfusion of blood products

- Disorders of Fibrinolysis:
  - plasminogen —tPA→ plasmin
    - cleaving fibrin & serum fibrinogen
    - destroying coagulation factors
    - blocking platelet aggregation
  - In these disorders, there is overactivity of plasmin
  - Example:
    - Radical prostatectomy
    - Cirrhosis of liver
  - These disorders resembling DIC in presentation