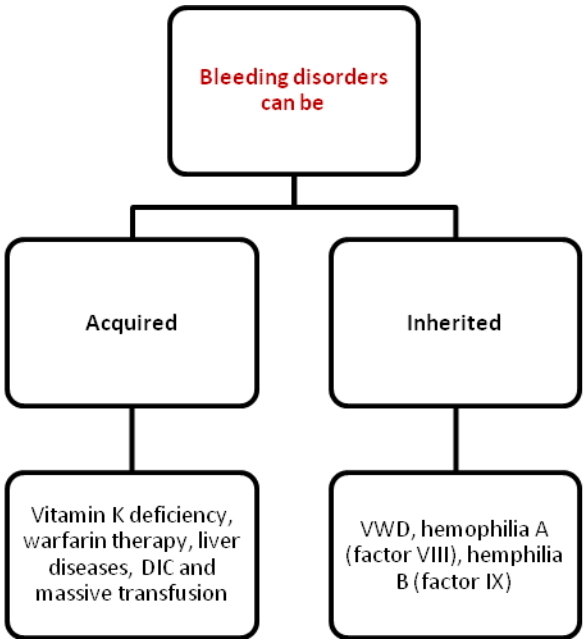
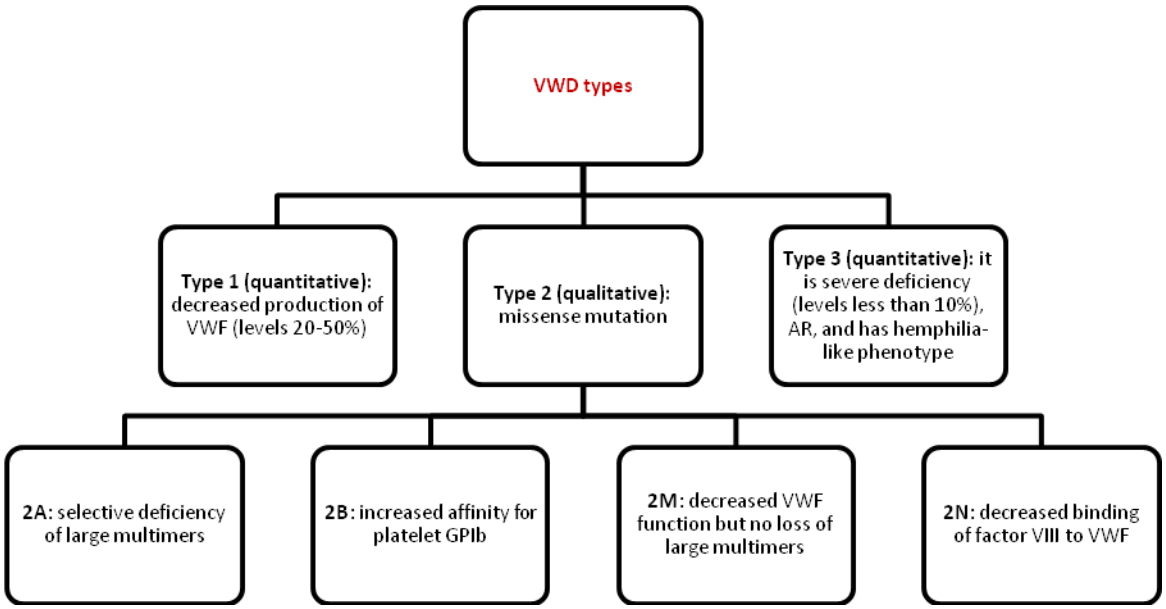
Problem 4 – Unit 6 – Biochemistry: genetics of inherited bleeding disorders

- **Classification of bleeding disorders can be:**
  - Vascular components/ platelet disorders.
  - Coagulation abnormalities.



- **Genetic factors:**
  - Mutations in single gene: causing loss of function.
  - Variant in genes: causing alteration of function.
  - Chromosomal imbalance: causes alteration in gene dosage.
    Note: disorders can be dominant (one copy affected) or recessive (two copies affected) or X-linked (one copy affected on X-chromosome).
- **The contribution of genetic and environmental factors:**
  - Duchenne muscular dystrophy is pure genetic.
  - Spina bifida: balanced between genetic and environmental factors.
- **Genetics of VWD:**
  - VWD is a common inherited bleeding disorder (autosomal dominant).
  - VWF gene is located on chromosome 12 containing 52 exons.
  - More than 500 mutations are defined in this gene. Partial lack of VWF causes mild to moderate bleeding disorder.
- **Common bleeding in VWD:**
  - Gyn/Obs 60% →menorrhagia has a good sensitivity but low specificity. Abnormal menstruation is characterized by:
    - ✓ 80 ml/month
    - ✓ Clots greater than 1 inch in diameter.
    - ✓ Low serum ferritin.
    - ✓ Changing the pad every one hour.
  - Nose 60% (common in children).
  - Teeth 50%
  - Ecchymosis 50% (easy bruising)
- **Lab investigations:**
  - ↑bleeding time, defective PFA-100, ↑PTT, ↓factor VIII, ↓ristocetin.



- **Inherited hemophilia A & B:**
  - Sex-linked (exclusively in men).
  - **There are two types:**
    - ✓ Deficiency in factor VIII → hemophilia A
    - ✓ Deficiency in factor IX → hemophilia B
  - **Factor level and severity:**
    - ✓ *<1%* : sever, bleeding after minimal injury.
    - ✓ *1%-5%*: moderate, bleeding after mild injury.
    - ✓ *5%*: mild, bleeding after significant trauma or surgery.
  - **Most hemophilia A cases are due to inversion mutation in intron 1 or 22:**
    - ✓ *Stop mutation*: preventing factor production.
    - ✓ *Missense mutation*: affecting factor activity no production.
  - **Treatment of hemophilia A:**
    - ✓ Doses of recombinant factor VIII, but with prolonged therapy antibodies will be produced against the factor so what we will do is:
      * Bypassing the factor to effect hemostasis with factor VIIa.
- **Other inherited factor deficiencies:**
  - **Factor XI**: mostly in Ashkenazi Jews. Bleeding is usually mild except after surgery or significant injury.