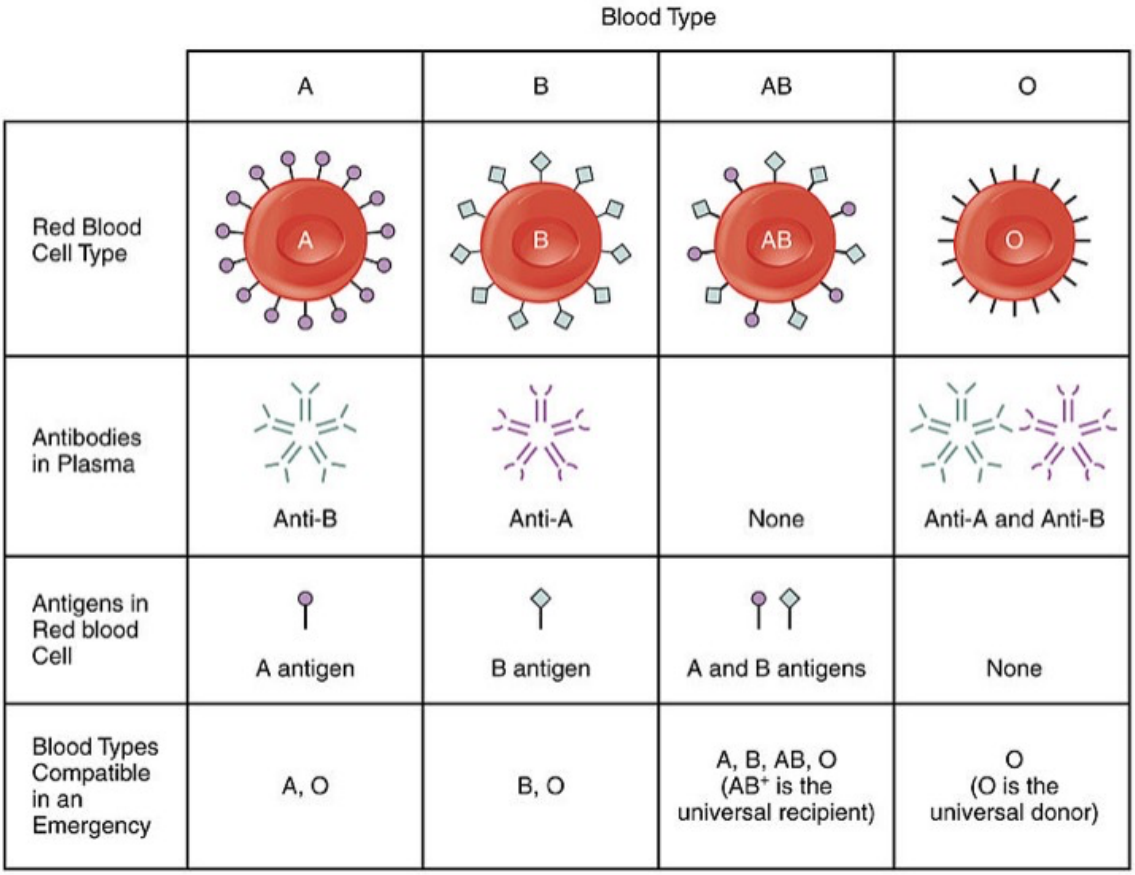
Haematology



Blood group O most common in UK

Clotting and coagulation

3 processes to stop bleeding

1. Vasoconstriction
2. Platelet aggregation
3. Blod clot / coagulation

<u>Platelets</u>

- Lifespan of 10 days
- 1/3 of platelets are held in the spleen
- Contain:
  - Dense granules - ADP, ATP, serotonin and calcium
  - Alpha granules - clotting factors, vWF, PDGF
  - Lysosomes - hydrolytic enzymes
- When meet collagen (e.g. vascular injury)

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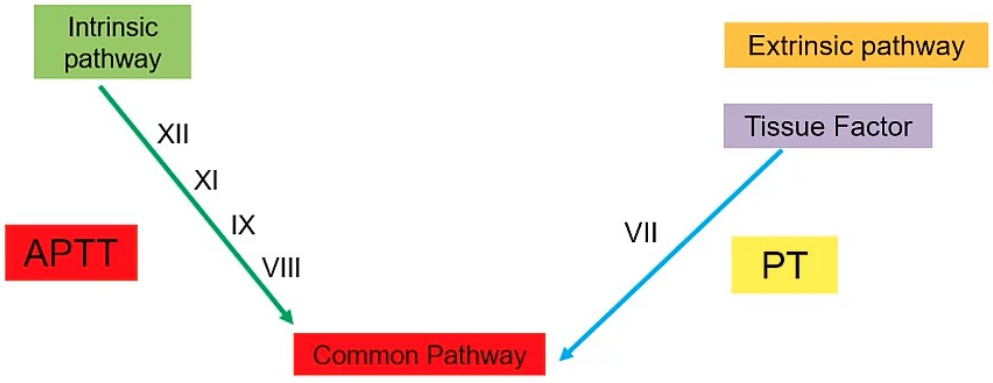
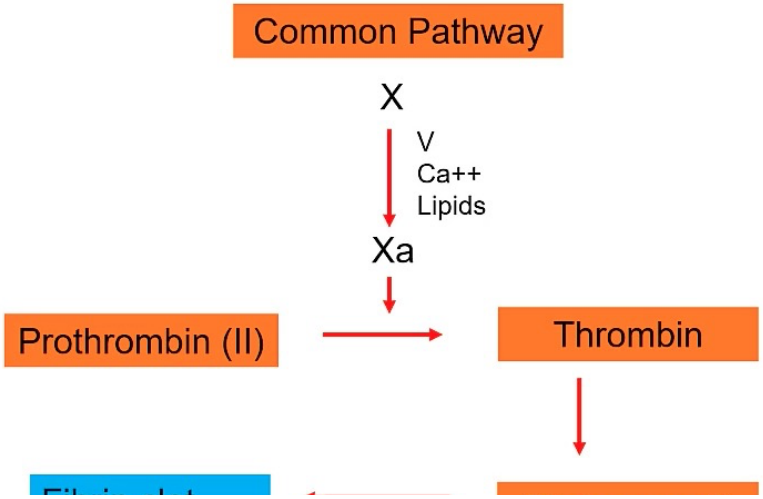
    - —> conformational change
    - —> TXA2 (thromboxane A2) and ADP release from granules
        - TXA2 released by platelets —> stimulates secondary amplification of platelets and aggregation
    - —> adheres to vessel and coagulation cascade begins

Platelet disorders

1. ↓ production - aplastic anaemia, myeloma, bone marrow suppression (chemo, infiltrates etc)
2. Destruction -
    - Immune mediated - ITP, SLE, heparin-induced thrombocytopenia (Ab produced against platelets)
    - Non immune - haemolytic uraemia syndrome, DIC
3. ↓ function - myeloproliferative disease, NSAIDs reduce platelet activity, advanced renal disease

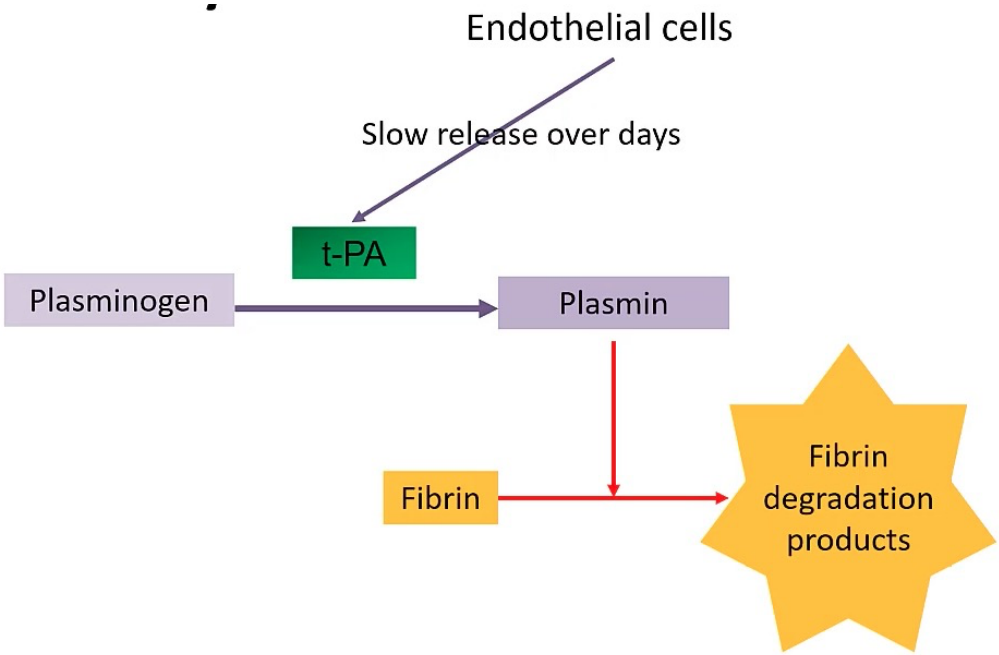
<u>Coagulation</u>

- Clotting factors made in the liver
- Vit K dépendant = II, VII, IX, X
- Extrinsic pathway: tissue factor = Factor III
    - Extrinsic pathway factors = III, VII, X
- Factor Xa = common pathway factor
    - Acts on prothrombin —> to create thrombin
    - 1 factor Xa can create 1000 molecules thrombin
    - Thrombin makes fibrinogen —> to fibrin
- 

- 

- PT = extrinsic pathway. *WEPT* = warfarin, extrinsic, PT. Is used for the INR
- APTT = intrinsic pathway, heparin
  - Haemophilia - factor 8 deficiency
  - Haemophilia B (Christmas disease) - factor 9 deficiency

Fibrinolysis



- Plasminogen is circulating normally in health - gets in amongst clots
- tPA builds up over several days —> will activate plasminogen around the clot —> becomes plasmin
- Plasmin then degrades fibrin
- TXA blocks the conversion of plasminogen to plasmin

Coagulation disorders

1. Congenital
   - Haemophilias
     - Haemophilia A - factor 8 deficiency (last factor in intrinsic pathway)
       - APTT and factor 8 direct measurement
       - Variable severity
       - Mainly only cause problems during surgery or trauma, may have spontaneous haemoarthroses
       - Recombinant factor 8 infusion if needed
     - Haemophilia B - factor 9 deficiency
       - Recombinant factor 9 infusion if needed
   - VW disease
     - Deficient or abnormal vWF
     - Less severe - epistaxis, GI bleed, mennorhagia
2. Acquired
   - Therapy
     - Warfarin, heparin, LMWH, DOACs

        - Heparin occurs naturally in mast cells
            - Binds antithrombin III —> heparin-antithrombin III complex binds factor Xa and inhibits it
            - Short half life, rapid onset - given by IV infusion
            - Protamine sulfate reverses
            - APTT
        - LMWH
            - More predictable vs unfractionated
            - Given by weight, OD - longer half life
            - Same mechanism as heparin
        - Fondaparinux
            - Xa inhibitor
            - Used in ACS, can be used as alternative to LWMH
                - Much lower risk of heparin induced thrompocytopaenia
        - Warfarin
            - FFP reversal when vit K too slow - rapid warfarin reversal (beriplex - II, VII, IX, and X)
            - Vit K for reversal also
        - DOACs
            - Direct factor IIa inhibitor - dabigatran
            - Direct factor Xa inhibitor - apixaban, rivaroxaban etc
            - Monitoring = specific anti-factor IIa and anti-factor Xa levels
                - APTT and PT poorly predictive of level of anti-coagulation
    - Liver disease
    - DIC

Thrombophilias

Cause ↑ risk of DVT, PE, clotting

- Inherited
    - Factor V leiden deficiency
    - Protein C and S deficiency (which neutralise clotting factors)
    - Antithrombin III deficiency
- Acquired
    - Antiphospholipid syndrome
    - SLE
    - Oral contraceptive pill
    - HRT
    - Polycythaemia
    - Malignancy
    - Pregnancy
    - Obesity

ANAEMIA

Hepcidin - reduces liver and macrophage iron release, reduces gut uptake of iron

Increased hepcidin = reduced iron

- RAISES HEPCIDIN
  - Inflammation / chronic disease / infection
- LOWERS HEPCIDIN
  - Low iron
  - Low O2
  - High EPO

Ferritin

- Stores iron in cells and found in serum - universally around tissue cytosol
- If low, then iron is low
- IDA vs chronic disease anaemia - ferritin to distinguish
  - ↓ in IDA
  - normal or ↑ in chronic disease anaemia

Transferrin

- Made in liver, TIBC refers to amount of transferrin available (same thing)
- Transports iron around the blood
- Iron overload = reduced transferrin
- Iron deficiency = increased transferrin

Reticulocytes

- Young, immature RBCs made by bone marrow. Do not have a cell nucleus, but have network of ribosomal RNA which makes Hb
- Normally 1-2% of RBCs are reticulocytes
- In response to anaemia
- If bone marrow failure, then anaemia **PLUS** (absolutely or relatively) low reticulocytes (as can't adequately make new RBCs)
- High reticulocytes
  - Haemolytic anaemia
- Low reticulocytes
  - BM failure/malignancy, aplastic anaemia, ↓ EPO production, B12/folate deficiency, other causes of poor RBC production

RBC recycling

- At 120 days - RBC broken down in bone marrow, liver and spleen
- Broken down (phagocytosed) by macrophages
- —> into 3 main components
  1. Heme groups —> bilverdin —> bilirubin
  2. Iron —> ferritin for liver storage and iron recycled for more erythropoeisis

3. Globin (protein) part of Hb —> broken down to amino acids for re-use

- **Microcytic**
  - Iron deficiency
    - Bleeding e.g. GI, menstruation
    - Malabsorption
  - Thalassaemia
- **Normocytic**
  - Anaemia of chronic disease
  - Bone marrow failure
  - Renal disease/failure (EPO)
  - Haemolysis
    - Jaundice, hepatosplenomegaly, gallstones (all due to ↑ bilirubin)
    - Normocytic or macrocytic anaemia - due to ↑ reticulocyte production
    - Causes
      1. Immune mediate (direct coombs +ve)
         - Drug induced - penicillins, quinolones
         - Autoimmune haemolytic anaemia
      2. Mechanical - e.g. prosthetic heart valves
      3. Hereditary:
         1. G6PD deficiency -
            - commonest RBC enzyme defect
            - prone to oxidative stress - unable to produce glutathione in RBCs
         2. Membrane defects - e.g. hereditary spherocytosis
         3. Haemoglobinopathies - thalassaemia and Sickle cell also predispose to shortened RBC lifespan
            - *Sickle cell* -
              - HbS instead of HbA = abnormal haemoglobin
              - Heterozygote = sickle cell trait, homozygote = sickle cell disease
              - Relative hypoxia —> the change in RBC shape —> cant pass through capillaries —> ischaemia —> sickle cell crises
                - Thrombotic crisis (from sickle cells occluding vasculature):
                  1. Strokes in children and adults
                  2. Painful bone crisis - generalised or local bony pains, abdominal crises, chest pain, neurological signs
                  3. Painful hands and feet, inflammation of end digits
                  4. Renal failure - due to renal infarction
                  5. Abdominal crisis - e.g. mesenteric ischaemia
                  6. Asceptic necrosis - femoral or humeral heads often
                - Sequestration
                  1. Acute chest syndrome - HYPOXIA —> SOB, worsening cough, chest pain, bilateral infiltrates

2. Sickling in liver, spleen —> can lead to auto-splenectomy
- Aplastic crisis: caused by parvovirus infection —> sudden fall in Hb
- Haemolytic anaemia (and all sx of anaemia)

- *Thalassaemia*
  - ↓ alpha or beta Hb chains
  - Beta thalassaemia
    - Thalassaemia minor
      - If one allele affected = thalassemia minor (one HbB missing) -
      - usually asymptomatic, anaemia >90 usually
      - Low MCV (<75), slight increase HbF
      - Often appears like IDA
    - Thalassaemia major
      - Both alleles affected - deficiency of both beta chains
      - Severe anaemia from childhood
      - Splenomegaly, iron overload

- TESTS - looking for agglutination of antibodies
  - Direct coombs -
    - tests if **RBCs** have antibodies already bound to them (causing haemolysis)
    - Haemolytic anaemia
  - Indirect coombs -
    - tests the **plasma** for antibodies. Take the patients plasma and test it against other RBCs.
    - testing in pregnancy before blood transfusion to prevent fatal haemolysis. Also used in process of cross matching
  - ↑ reticulocytes (newly formed young RBCs)
  - ↑ bilirubin - unconjugated
  - LDH

- **Macrocytic**
  - *B12 and folate deficiency characteristics:*
    - Hyper-segmented neutrophils
    - Megalobasts (which are large, immature and dysfunctional RBCs
    - B12 deficiency - ?IF deficiency ?parietal cell anti-bodies
  - Folate deficiency -
    - Mainly women and children (times of growth when a lot of DNA is required)
    - Phenytoin and alcohol can exacerbate
    - Coeliac and crohn's disease can cause
  - B12 deficiency (cobalamin)
    - Mainly elderly
    - Produced by bacteria in soil —> grass eating animals —> meat for humans
    - Limited by amount of IF - made by parietal cells
      - IF + B12 in stomach —> travels through to terminal ileum together for absorption
    - Normal body stores are sufficient for **4 years**
    - Causes
      - Dietary lack

        - Dietary lack
        - GI malabsorption - e.g. coeliac, terminal ileum disease in IBD
    - Presentation
        - Neuropsychiatric - depression, dementia, confusion, psychosis
        - Neurological - loss of myelin in spinal cord (subacute combined demyelination of spinal cord)
            - Sensory, motor, and dorsal column disturbance
            - Reversible if treated but will become permanent if not treated
            - MUST GIVE B12 + FOLATE TOGETHER if both low
- Alcohol and liver disease
- Reticulocytosis (because reticulocytes = young RBCs = larger cells)
- Pregnancy