- Removal of these inclusions by the spleen results in Red Blood Cell Membrane Damage and Reduction in Red Blood Cell Survival

Inherited Haemolytic Anaemias:

- Enzyme Deficiencies:
  - **Glucose 6-Phosphate Dehydrogenase Deficiency:**
    - Affects the **Pentose Phosphate Pathway**
    - G6PD is a enzyme required for the production of NADPH which is essential for maintaining the Glutathione of Red Blood Cell Membrane in the reduced state
    - Deficiency in reduced Glutathione causes **susceptibility of Red Cell to Oxidative Stress**
      - Therefore taken out of Circulation as they are easily Damaged
    - Most Common Haemolytic Disorder
    - **X-linked Disorder**
      - Full Expression in Males
      - Females are carriers with 50% reduction in G6PD Levels
    - Diagnosis:
      - Low G6PD Levels
    - Treatment:
      - Avoidance of Oxidant Drugs and prompt management of infection
  - **Pyruvate Kinase Deficiency:**
    - Pyruvate Kinase catalysis the final step in the **Glycolytic pathway**
    - Pyruvate Kinase Deficiency leads to Chronic non-spherocytic Haemolytic Anaemia with Extravascular Haemolysis
    - **Autosomal Recessive Disorder**
    - Clinical Features:
      - Neonatal Jaundice & Anaemia
      - Chronic non-spherocytic Haemolytic Anaemia (CNSHA)
      - Compensated Haemolysis
    - Lab Diagnosis:
      - Normochromic Anaemia with reticulocytosis, acinocytosis and poikilocytosis
      - Increase in MCHC due to Dehydration Brought by ATP deficiency
    - Management:
      - Splenectomy in patients with severe haemolysis
  - **Hereditary Spherocytosis:**
    - Haemolytic Disorder due to **defects in the proteins which connect the underlying Cytoskeleton to the lipid bilayer if the membrane**
    - These Cell's membranes become more rigid and are **unable to pass through the spleen** and therefore have a Decreased Lifespan
    - **Autosomal Dominant** Condition
    - Clinical Presentation:
      - Anaemia with episodes of Haemolysis presenting with Jaundice
      - Jaundice may lead to Gallstones in long-term
      - Folate deficiency due to Chronic Haemolysis
      - Splenomegaly → Splenectomy reverses mechanisms of Cell destruction and alleviates Anaemia
    - Lab Findings:
      - Spherical shaped Red Blood Cells
      - Peripheral Blood Smear:
        - Microspherocytes with polychromasia
      - Negative Coombs Test
      - MCHC is Increased

        - Red blood Cell Membrane is altered when a Drug binds to it and becomes antigenic leading to antibody-mediated Haemolysis
            - E.g. Cephalosporin
    - **Drug-induced Autoantibody Mechanism:**
        - Associated with chronic intake drugs where stimulation of antibodies with specificity for Red Blood Cell Membrane
- **Paroxysmal Nocturnal Haemoglobinuria (PNH):**
    - Rare condition
    - Patients **Red Blood Cells are sensitive to Lysis by Complement** in normal Plasma
    - Characterised by Haemolysis after sleeping and resulting in Dark Urine due to Haemoglobinuria in the morning.
    - Result of an **Acquired Mutation** in the Gene on the **X-chromosome**
    - This results in the cell lacking GPI protein on their surface and therefore results in Haemolysis
    - Clinical Findings:
        - Passage of Dark Urine after waking due to Haemolysis
        - Jaundice
        - Thrombosis
        - Cytopenias
    - Lab Findings:
        - Anaemia and Thrombocytopenia
        - Increased LDH and Unconjugated Bilirubin
        - Decreased Haptoglobin
        - Haemosiderinuria
- **Microangiopathic Haemolytic Anaemia: (MAHA)**
    - Collectively a **group of conditions** which fall under the Microangiopathic Haemolytic Anaemias constitute the most frequent causes of Haemolysis:
        - Disseminated Intravascular Coagulopathy (DIC)
        - Thrombotic Thrombocytopenic Purpura (TTP)
            - Clotting in Small Blood Vessels resulting in Low Platelet Count
        - Haemolytic Uraemic Syndrome (HUS)
        - Vasculitis
        - Pre-eclampsia
        - Mechanical Heart Valves
        - Disseminated Malignancy
        - Glomerulonephritis
        - Malignant Hypertension

Disorders of Haemoglobin

- Haemoglobin Abnormalities:
    - Synthesis of Abnormal Haemoglobin – most commonly due to Amino Acid Substitution
    - Reduced Rate of Synthesis of Normal Alpha or Beta Globin Chains – a heterozygous group of Disorders (Thalassamias)

Sickle Cell Disease:

- Inherited Chronic Haemolytic Anaemia
    - **Autosomal Recessive**
- Arises due to the deficiency of the Sickle Haemoglobin (HbS) to polymerise and deform Red Cells to Sickle Shaped
- This is due to an inheritance mutation which produces an **abnormality of the Beta Globin Chain**