CLINICAL HAEMATOLOGY NOTES

PRE-SUMMARIZED
READY-TO-STUDY
HIGH-YIELD NOTES

FOR THE TIME-POOR
MEDICAL, PRE-MED,
USMLE OR PA STUDENT

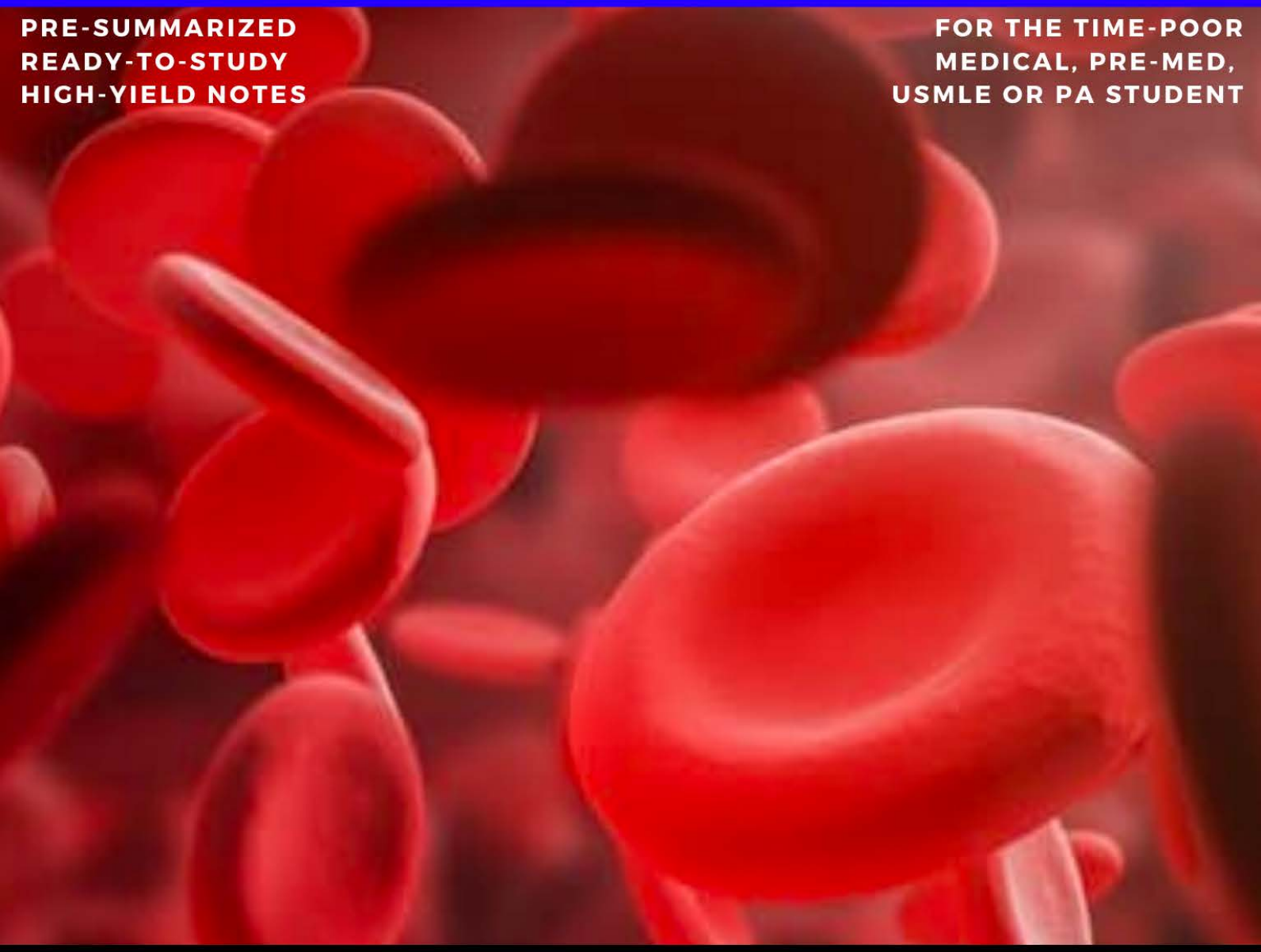

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Table Of Contents:

What's included: Ready-to-study anatomy, physiology and pathology notes of the haematological system presented in succinct, intuitive and richly illustrated downloadable PDF documents. Once downloaded, you may choose to either print and bind them, or make annotations digitally on your ipad or tablet PC.

Free bonus: 'Hematology' chapter of Toronto Notes for reference and further detailed reading.

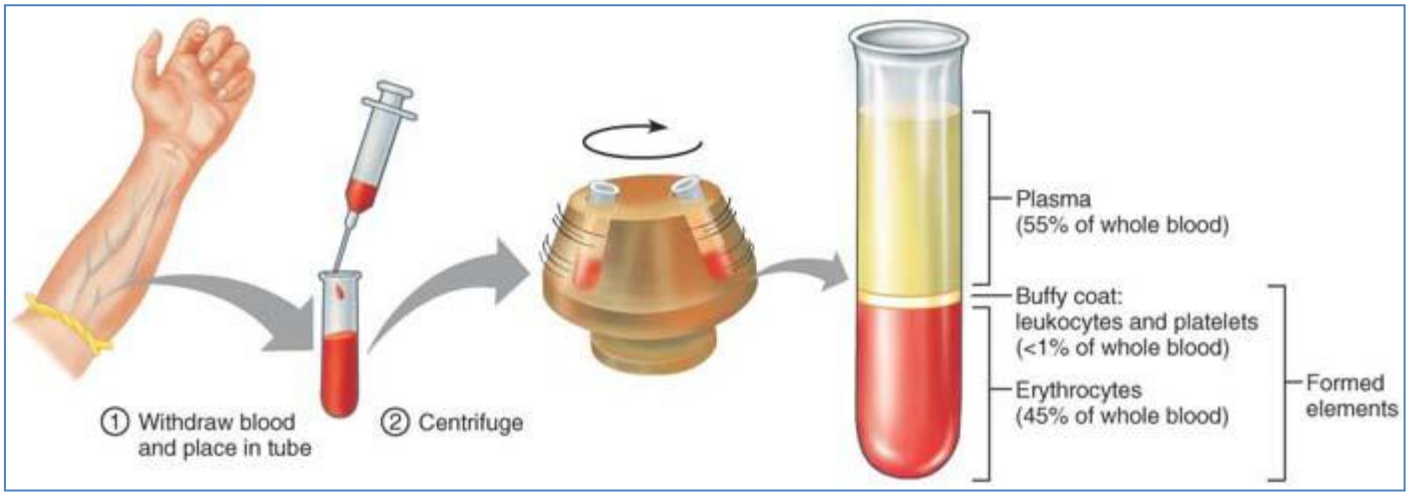
File List:

Blood: An Overview:

- The main transport medium of the body
- 7% of body weight
- A special type of *Connective Tissue* (living cells suspended in a non-living matrix)
- Exits the *Heart* via *arteries*, which branch into capillaries.
    - Oxygen & nutrients diffuse into body tissues & CO_2 and wastes diffuses into the bloodstream.
        - This blood leaves the capillaries → Veins → heart → Lungs
- More dense than water
- 5x more viscous than water
- pH beween 7.35 & 7.45
- 38 degrees celcius
- Around 5L of blood in body

- **Functions:**
    - **Distribution:**
        - Oxygen
        - Metabolic Waste
        - Hormones
    - **Regulation:**
        - Temperature
        - Maintaining pH in body tissues.
        - Fluid volume in Circulatory System
    - **Protection:**
        - Preventing blood loss – clotting
        - Preventing infection

- **Components:**
    - Mixture of Cellular & Liquid
    - In a Centrifuged Sample:
        - Red Blood Cells (Erythrocytes) sink to the bottom (heaviest)
            - Normally 45%$^{+/-}$ of the total blood-volume (a measure known as the **Hematocrit**)
        - White Blood Cells (Leukocytes) & Platelets form the "Buffy Coat" in the middle.
        - A layer of plasma 'floats' on top. (Mostly water)



- **Plasma:**
  - Straw-coloured, sticky fluid
  - Mostly water (90%)
  - Contains 100's of dissolved nutrients/gases/hormones/wases/ions/protein
  - 5-7% protein:
    - Albumin – blood carrier
    - Globulin – mainly immunoglobulins
    - Fibrinogen – part of a clotting protein
  - Predominate Ions: Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl-, HCO3-

- **Serum:**
  - The fluid, noncellular portion of blood that remains after coagulation; lymphatic fluid.
  - Serum is equivalent to plasma without its clotting elements.

- **Cells:**
  - **Red Blood Cells**: AKA: Erythrocytes - carry oxygen around the body

  - **White Blood Cells:** AKA: Leukocytes: (leuko = white)
    - **Granulocytes:** (due to cytoplasmic granules)[are *polymorphonuclear* – Multilobed Nucleus]
      - **60% Neurtophils** - Responsible for fighting bacterial infections & some cancers
      - **3% Eosinophils** - Responsible for fighting parasitic infections & also allergic reactions
      - **0.5% Basophils** - Responsible for allergic reactions

    - **Non-Granulocytes:**
      - **5% Monocytes -** 2 functions:
        - Replenish resident macrophages and dendritic cells under normal states
        - In response to inflammation signals, migrate to sites of infection in the tissues and divide/differentiate into macrophages and dendritic cells to elicit an immune response.
      - **30% Lymphocytes** - Constantly circulating -Responsible for innate immune response (T-cells, B-cells & NK-cells)
        - **T-Lymphocytes:** Responsible for *Cell-Mediated* immune response.
        - **B-Lymphocytes:** Responsible for *Humoral* immune response by producing antibodies.

  - **Platelets:** From fragmented Megakaryocytes – Responsible for Clotting.

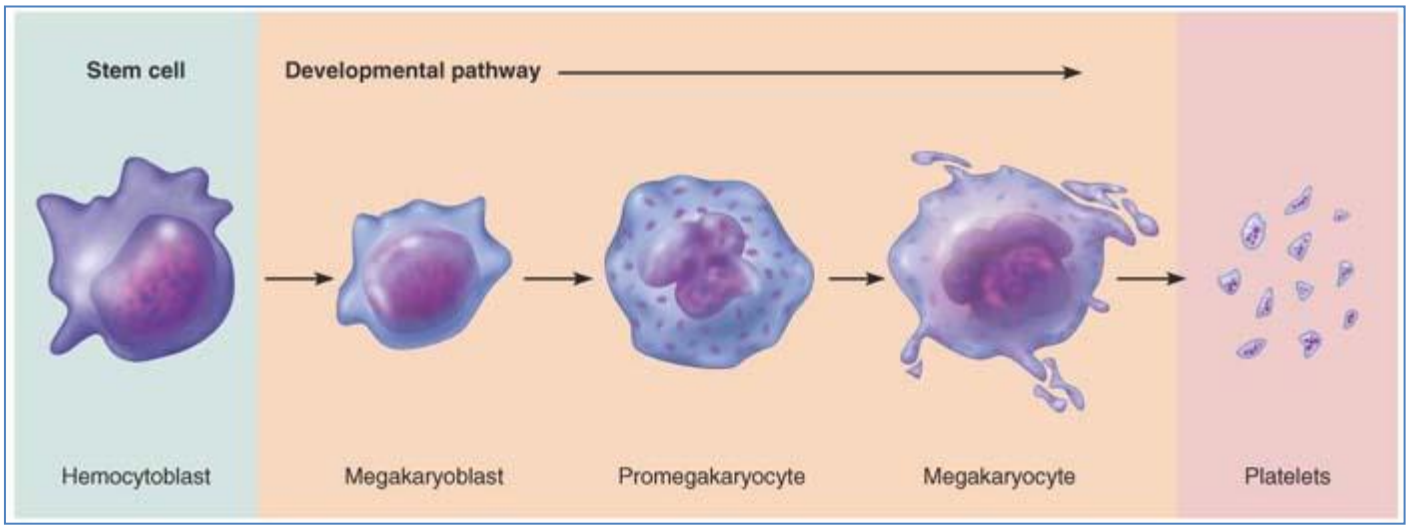


TABLE 17.2 Summary of Formed Elements of the Blood

CELL TYPE	ILLUSTRATION	DESCRIPTION*	CELLS/μl (mm^3) OF BLOOD	DURATION OF DEVELOPMENT (D) AND LIFE SPAN (LS)	FUNCTION
Erythrocytes (red blood cells, RBCs)		Biconcave, anucleate disc; salmon-colored; diameter 7–8 μm	4–6 million	D: about 15 days LS: 100–120 days	Transport oxygen and carbon dioxide
Leukocytes (white blood cells, WBCs)		Spherical, nucleated cells	4800–10,800		
Granulocytes					
▪ Neutrophil		Nucleus multilobed; inconspicuous cytoplasmic granules; diameter 10–12 μm	3000–7000	D: about 14 days LS: 6 hours to a few days	Phagocytize bacteria
▪ Eosinophil		Nucleus bilobed; red cytoplasmic granules; diameter 10–14 μm	100–400	D: about 14 days LS: about 5 days	Kill parasitic worms; destroy antigen-antibody complexes; inactivate some inflammatory chemicals of allergy
▪ Basophil		Nucleus lobed; large purplish-black cytoplasmic granules; diameter 10–14 μm	20–50	D: 1–7 days LS: a few hours to a few days	Release histamine and other mediators of inflammation; contain heparin, an anticoagulant
Agranulocytes					
▪ Lymphocyte		Nucleus spherical or indented; pale blue cytoplasm; diameter 5–17 μm	1500–3000	D: days to weeks LS: hours to years	Mount immune response by direct cell attack or via antibodies
▪ Monocyte		Nucleus U or kidney shaped; gray-blue cytoplasm; diameter 14–24 μm	100–700	D: 2–3 days LS: months	Phagocytosis; develop into macrophages in the tissues
Platelets		Discoid cytoplasmic fragments containing granules; stain deep purple; diameter 2–4 μm	150,000–400,000	D: 4–5 days LS: 5–10 days	Seal small tears in blood vessels; instrumental in blood clotting

*Appearance when stained with Wright's stain.

Sites of Formation of:

- Erythrocytes

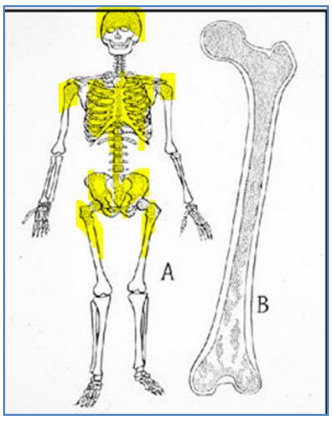
  Foetus 0 – 2 months – yolk sac
  2 – 7 months – liver, spleen
  5 – 9 months - bone marrow, liver

  Infants Bone marrow (most bones)

  Adults Vertebrae, ribs, sternum, skull, sacrum and pelvis, proximal end of femur

Liver and spleen can be sites of production of erythrocytes (*extramedullary erythropoiesis*) at times of extreme demand

Eg. During anaemia

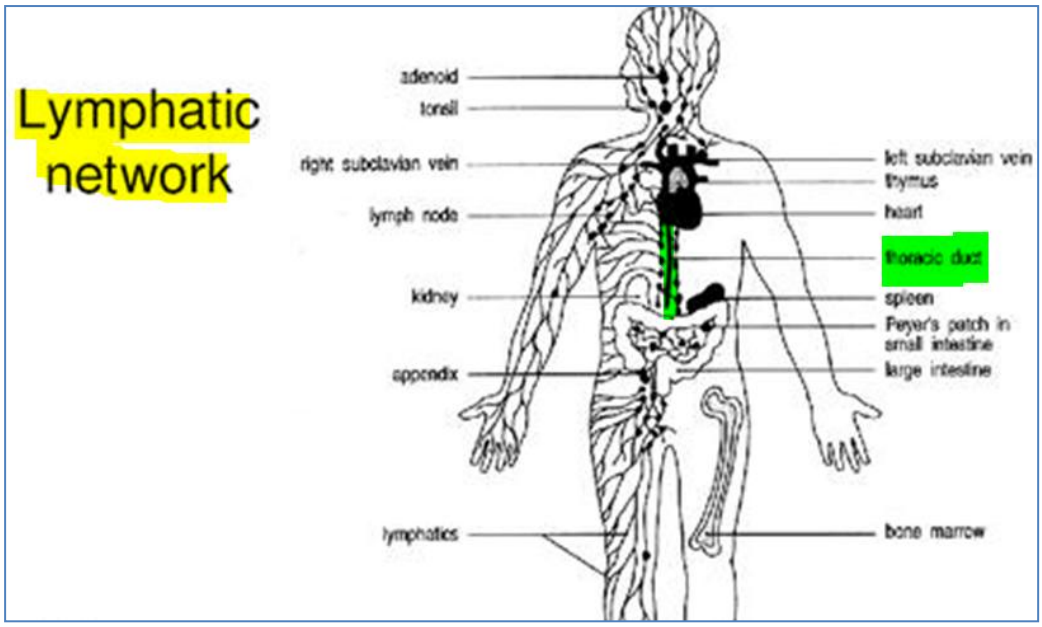


- Leukocytes
  - Granulocytes and monocytes are formed in the bone marrow from a common precursor cell (*Myeloid lineage*)

- Lymphocytes are formed in the bone marrow and thymus (*primary lymphoid organs*) and spleen, lymph nodes, tonsils, adenoids and Peyer's patches (*secondary lymphoid organs*)

Lymphocyte Circulation:

- Lymphocytes circulate between blood & lymph
- Via a network of small lymphatic vessels
  - Collect interstitial fluid & return it to the large veins near the heart
  - Connect to a chain of lymph nodes & organs within the Lymphatic Network:
- If there is an inflammation, lymphocytes stop in a regional node, proliferate & take part in immune response.



- How would you explain to the patient that lymph did indeed have an important function in the body?
  - It is responsible for the removal of interstitial fluid from tissues. It absorbs and transports fatty acids and fats as chyle (lymph & emulsified fats) to the circulatory system. The last function of the lymphatic system is the transport of antigen presenting cells (APCs), such as dendritic cells, to the lymph nodes where an immune response is stimulated.
  - As it flows through the lymph nodes, however, it comes in contact with blood and tends to accumulate more cells (particularly lymphocytes) and proteins.
  - It is also a medium for hormonal signalling - ie. Lympahtics draining the testes will have high levels of testosterone.

GLS Questions:

Spleen:

- Why does the spleen have a *nodular appearance*?
  - The white pulp of the spleen is composed of Nodules called *Malpighian Corpuscles*. These are composed of Lymphoid Follicles (rich in B-Lymphocytes) and *Periarteriolar Lymphoid Sheaths* ((PALs) rich in T-Lymphocytes.)
- What are the features that distinguish *white pulp* from *red pulp* in the spleen?

White	Function: mechanical filtration of red blood cells.	Composition: Sinuses (sinusoids) filled with blood, Splenic Cords of reticular fibres & a Marginal Zone bordering on white pulp.
Red		Composition: Nodules (Malpighian Corpuscles) made up of Lymphoid Follicles [rich in B-Lymphocytes] & Periarteriolar Lymphoid Sheaths (PALS) [rich in T-Lymphocytes].

Lymph Node:

- What is the difference between the cortex & medulla of a lymph node?
  - The Cortex contains numerous lymphoid follicles.
  - The Medulla has a meshwork-like morphology
- Where in a lymph node does lymph enter the node and where does it leave the node?
  - Lymph enters through the afferent lymphatics through the pericapsular connective tissue, perculates through the cortex & exits through efferent lymphatics located at the hilum.

Tonsil:

- What are tonsils?
  - The Tonsils are modified lymph nodes with a surface epithelium of squamous cells at the interface between the gland and the mouth lumen.

Thymus:

- What type of cell is found in *Hassall's Corpuscles?*
  - Clusters of keratinizing epithelial cells with central cellular debris, thought to be end-stage medullary cells involved in the destruction of thymocytes.

System: Haematological

Blood: An Overview:

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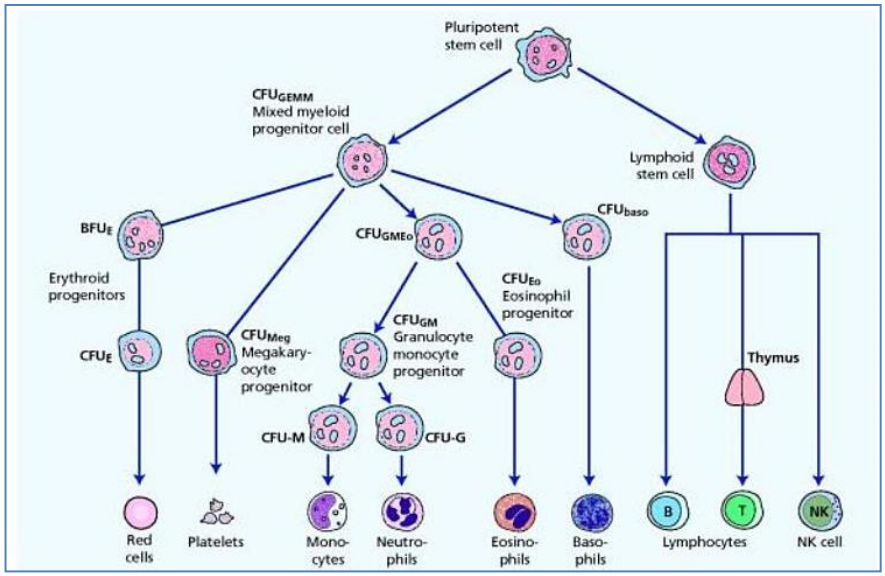
Haematopoiesis:

- 'The Formation of Cells in the Blood'
- Foetal Life: Takes place in the Yolk Sac/Liver/Spleen/&Bone Marrow.
- Childhood→Adult: Takes place only in the **Bone Marrow** (Medullary Cavity)
    - Ie. The Bone Marrow is the only source of *new blood cells*.

Haematopoietic Stem Cells:

- Haematopoiesis starts with ***PluriPotent Stem Cells*** in the bone marrow.
- Self-renewing
- Differentiate & Divide to give rise to the separate cell lineages.
    - Erythroid → RBCs
    - Granulocytic → Granulocytes (Neutrophils/Eosinophils/Basophils)
    - Monocytic → Macrophages
    - Megakaryocytic → Platelets
    - Lymphoid → Lymphocytes (T&B)
    - Etc…see diagram.
- Leukemias can result from defective haematopoietic stem cell lines;
    - Some people may need bone marrow transplants to replace/regenerate the stem cell pool.



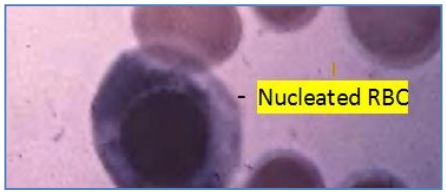
Erythropoiesis:

- Red Blood Cell Formation
- A sequence of *Amplification* & *Maturation*.
    - Stem Cells → CFU's → BFU's →The 1st recognisable erythrocyte precursor: The **Pronormoblast.**
        - Pronormoblast → progressively smaller Normoblasts → **Reticulocytes** (no nucleus – but DNA & RNA remnants)

NB$_1$: As erythrocyte precursors mature, they ***gain haemoglobin*** & ***lose nuclear material.***

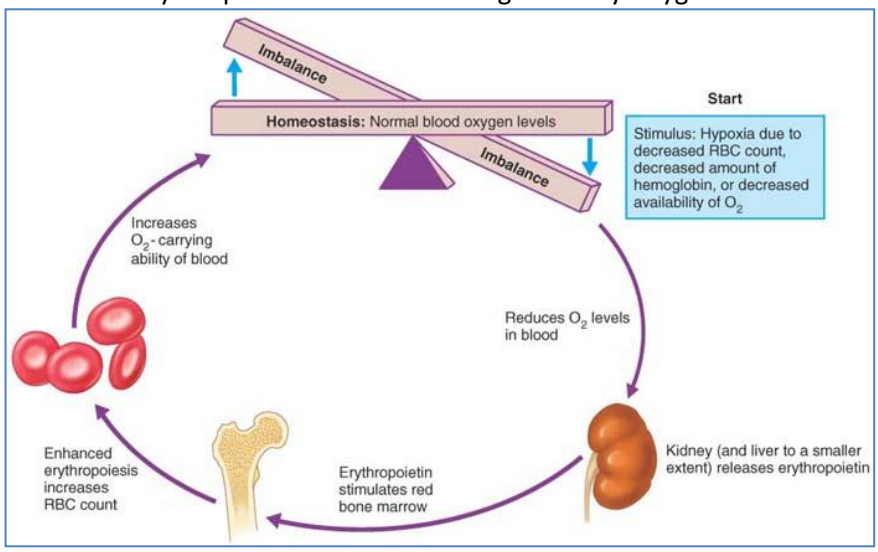
NB$_2$: Reticulocytes circulate in peripheral blood (1-2 days) before maturing in the *Spleen*.

NB$_3$: Excess Reticulocytes in blood can be indicative of Anaemia (ie. The body's effort to compensate for lack of O_2)



NB$_4$: Severe Anaemia can result in nucleated RBC's in the blood (not good)

- **Erythropoietin:**
  - Erythropoiesis is regulated by the ***Hormone 'Erythropoietin'***
    - Produced by the *PeriTubular Interstitial Cells* of the *Kidneys*. (Also produced by liver <10%)
      - Erythropoietin Production – regulated by Oxygenation of Tissues in Kidneys.



Requirements for Erythropoiesis & Haemoglobin Formation:

- The *Marrow* requires other precursors for effective erythropoiesis: eg.
  - **Metals:**
    - Iron – essential for Haemoglobin synthesis
  - **Vitamins:**
    - Especially Vit. B_{12} - necessary for normal DNA synthesis
    - Folate - necessary for normal DNA synthesis
  - **Amino Acids:**
    - For the production of proteins
  - **Hormones:**
    - ***Erythropoietin***

Haemoglobin:

- **Functions:**
  - To carry O_2 to tissues
  - To Return CO_2 from tissues → Lung
  - Storage pool of Iron. (65% of bodily Iron is in Haemoglobin)
- **Constituents:**
  - Made up of the protein ***globin*** bound to the red ***heme*** pigment.
  - *Globin* consists of *4 Polypeptide Globulin* chains – each with its own *Haem Group*.
    - 2 Alpha
    - 2 Beta
  - Haem Molecules (Groups)....containing:
    - Protoporphyrin:
    - 1x Iron atom in its centre:
- **Oxygen Loading:**
  - In lungs
  - Haemoglobin → Becomes **OxyHaemoglobin**:
- **Oxygen UnLoading:**
  - In Tissues
  - OxyHaemoglobin → Becomes **DeOxyHaemoglobin:**
- **CO_2 Transport:**
  - CO_2 binds to Globin's Amino Acids ...Rather than on the Haem Group.

Erythrocyte Death:

- Average Erythrocyte Lifespan: 120 Days
- Dying Cells – Removed by Macrophages in Spleen & Liver
  - Iron is reused → Back to Bone Marrow (bound to *Transferrin*) → Stored as *Ferritin* in Bone Marrow.
  - Protoporphyrin (Haeme minus Iron) is metabolized → Bilirubin → Conjugated in Liver → Bile.

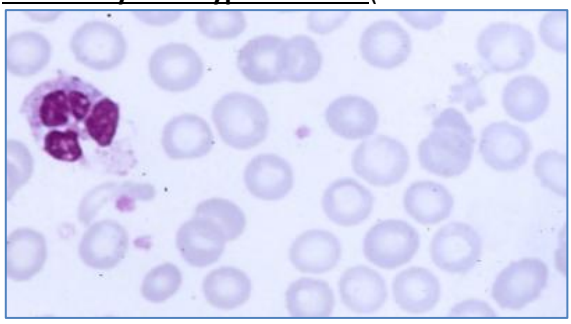
Anaemia

Introduction to Anaemia:

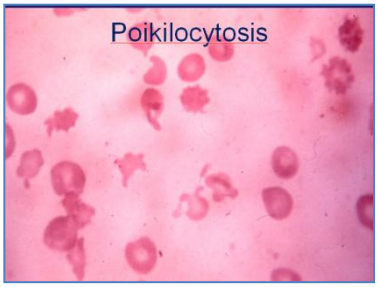
- **Definition:** ***A Lower-Than-Normal Haemoglobin Concentration.*** (generally less than 100g/L)

3 Common Anaemic Combinations:

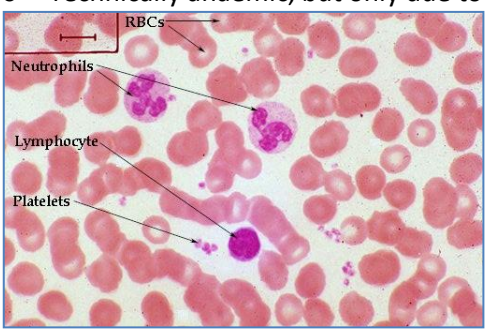
- **1. Microcytic & Hypochromic:** (Small & Non-Staining)



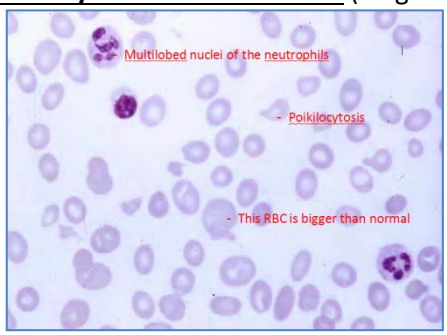
  - **Iron Deficiency (Typically):**
    - Low Iron Stores
    - Commonest cause of Anaemia
    - Iron is needed for Haemoglobin production (& RBC production)
    - ↓Iron Stores → ↓Erythropoiesis
  - **Chronic Inflammation:**
    - Lack of Fe Release from Macrophages in Bone Marrow → Plasma
    - ↓RBC lifespan
    - ↓Erythropoietin Response → ↓Erythropoiesis
  - **Sideroblastic Anaemia:**
    - Failure of Protoporphyrin synthesis (precursor of Heme)
  - **Thalassaemias:**
    - ↓ Synthesis of Alpha/Beta Globin chains – Haemoglobin Disorder - Ineffective erythropoiesis
    - ↑ Haemolysis – due to aggregation of unmatched globin chains
    - May exhibit *Poikilocytosis* (RBCs – weird shapes/sizes)
    - **Alpha Thalassaemia:**
      - Deletion of 1/more of the 4 Alpha Globin genes.
    - **Beta Thalassaemia:**
      - Mutations in the Beta Globin genes – prevent B-chain formation.



- **2. Normocytic & Normochromic:** (Normal Size & Colour)
  - Typically from Acute Blood Loss
  - Technically anaemic, but only due to ↓ Blood Volume



- **3. Macrocytic & Normochromic:** (Large & Normal Colour)

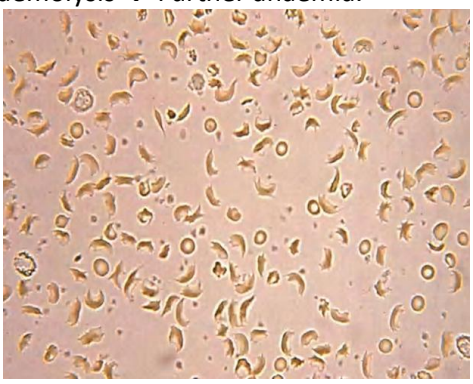


  - Typically from defective nuclear maturation of erythroblasts.
    - Due to defective DNA synthesis
      - Due to ↓$VitB_{12}$/Folate
  - Another cause: Alcoholism
  - **Causes of $VitB_{12}$ Deficiency:**
    - **Nutritional** – Lack of V_{B12} Dietary Intake.
    - **Gastric** – Abnormality of *Intrinsic Factor* (Eg. Perncious Anaemia – autoimmune response to parietal cells of stomach →↓IF →↓$VitB_{12}$ Absorption)
    - **Intestinal –** eg. Resected Ileum/Crohn's Disease
  - **Causes of Folate Deficiency:**
    - **Nutritional** – Lack of Folate Dietary Intake
    - **Malabsorption –** eg. Coeliac Disease/Intestinal Resection.
    - **Excess Utilization –** eg. Pregnancy/Lactation/Chronic Inflammation/Cancers
    - **Excess Urinary Loss –** eg. Acute Liver Disease/Congestive Heart Disease.

Other Anaemias:

- **Haemolytic Anaemia:**
  - Abnormal *Destruction* of RBCs
  - Where RBC lifespan ↓↓ & Bone-Marrow RBC Production can't keep up.
  - **Causes:**
    - Other Anaemias – eg. Macrocytic/Thalassaemias
    - **Inherited:**
      - Cell Membrane Defect – eg. Elyptocytosis
      - Naemoglobin – Thalassaemias/Sickling Disorders
      - Metabolic Disorders – G6P-Dehydrogenase Deficiency / Pyr.Kinase Deficiency
    - **Acquired:**
      - Immune – Autoimmune Haemolytic Anaemia
      - Isoimmune – Blood-Type Incompatibility (eg. Transfusion Reaction)
      - Non-Immune – Infection/Drug Side Effects/Hypersplenism (Hyperactive Spleen)
  - **Results:**
    - Elevated Free-Hb in Blood (*Haemoglobinaemia*)
    - Hb in Urine (*Haemoglobinuria*) → Red-Brown Urine.
    - Haemosiderin (iron from Hb) in Urine (*Haemosiderinurial*)

- **Sickle Cell Anaemia:**
  - Inherited
  - Prevalent in Afro-Carribean populations.
  - Abnormal Beta-Haemoglobin Chain
    - Abnormal Hb – Insoluble – Forms crystals @ low O_2 Tension
    - Leads to sickle-shaped RBC → Clogs small capillaries → Tissue Necrosis.
    - Episodes of haemolysis → Further anaemia.



Measuring Anaemia:

- **Via Red Cell Indexes:**
  - **Mean Cell Volume (MCV):**
    - Average size of RBC
    - Described as:
      - Microcytic (smaller than normal)
      - Normal
      - Macrocytic (larger than normal)
  - **Mean Cell Haemoglobin (MCH):**
    - The average *amount of haemoglobin in the average RBC*.
  - **Mean Cell Haemoglobin Concentration (MCHC):**
    - The average *concentration of haemoglobin in a given volume of blood*.
- **Staining:**
  - Normal RBCs stain well – **(Normochromic)**
  - Anaemic cells stain lightly - **(Hypochromic)**
- **Morphological Classification (Size):**
  - **Microcytic:** Small - Reduced MCV
  - **Normocytic:** Normal MCV
  - **Macrocytic:** Large – Increased MCV

Polycythaemia:

- **2 Types:**
  - **Absolute Polycythemia:** An increase in red cell mass caused by increased erythropoiesis, which may occur as a compensatory physiologic response to tissue hypoxia or as the principal manifestation of polycythemia vera.
  - **Relative Polycythemia:** A decrease in plasma volume without change in red blood cell mass so that the erythrocytes become more concentrated (elevated hematocrit), which may be an acute transient or a chronic condition.

Haemolytic Disease of the Newborn:

- **What is it?**
  - Condition that develops **in a foetus**, when the **Mother's IgG Anti-RhD Antibodies** crosses the placenta →Foetal Circulation.
  - →Attacks the red blood cells in the foetal circulation.
  - The RBC's are broken down and the foetus can develop reticulocytosis and anaemia → Death.
- **Pathogenesis:**
  - **Mother is usually O-Negative.**
    - Will have Anti-A & Anti-B Antibodies
    - BUT..unless she's been exposed to the RhD-Antigen, she won't have Anti-D Antibodies.
  - **During Pregnancy:**
    - 1. Sometimes Foetal Blood Mixes with Maternal Blood (eg. Placental Injury/Amniocentesis)
    - 2. If Foetal Blood is *Positive*, The Mother's Immune System Sensitizes to the RhD-Antigen.
    - 3. Maternal Immune system produces Anti-D Antibodies.
    - 4. These Maternal Immune Antibodies ('IgG'-Ab's) can cross the Placenta → Foetus.
    - 5. Antibodies Attack Foetal RBCs → Haemolysis.
    - 6. Excess Haemolysis may lead to Jaundice (Haem → Bilirubin)
- **Lab Findings:**
  - **Cord Blood:**
    - Rh-D Antigen Present (Positive)
    - Positive Direct Coomb's Test (ie. Mother's Anti-D Antibodies detected on Foetal RBCs)
    - ↑ Bilirubin
  - **Maternal Blood:**
    - Rh-D Antigen Absent (Negative)
    - Positive Indirect Coomb's Test (ie. High levels of maternal serum Anti-D Antibodies)
- **Prophylaxis Against Rh Sensitization:**
  - Passive administration of Exogenous Rh-D-Antibodies into mother can prevent the Primary Immune Response from occurring in the first place.
  - Ie. The Exogenous Rh-D-Antibodies destroy any foetal Rh-Positive Blood cells (that cross the placenta) before the immune system has time to become sensitized.

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Malignant Lymphomas:

- **2 Groups:**
    - **Hodgkin's Lymphoma:**
        - **Characterized By:**
            - The presence of Reed-Sternberg cells (RS cells).
                - (Bi/Multi-Nucleated Cells derived from lymphoid cells)
            - & the spread of disease from one lymph node group to another →the development of systemic symptoms with advanced disease.
        - **Most Common In Males:**
            - Young Adulthood (15-35)
            - Late Adulthood (55+)
        - **Clinical Signs:**
            - Asymmetrical & Painless Lymphadenopathy (Lymph Node Swelling)
            - Fever
            - Sweating
            - Weight Loss
            - Fatigue
        - **Diagnosis:**
            - Definitive diagnosis is by lymph node biopsy (Usually excisional biopsy with microscopic examination).
            - →Presence of 'RS Cells'
        - **Treatment:**
            - Radiation Therapy OR
            - Chemotherapy
                - Depending on Age.

    - **Non-Hodgkin's Lymphomas:**
        - **What Are They?:**
            - Diverse group of Haematologic Cancers, Encompassing Any Lymphoma *other than* Hodgkin's Lymphoma.
            - Complicated Classification.
            - Occur At Any Age.
            - May be Aggressive/Benign
        - **Clinical Signs:**
            - Initially Painless Lymphadeopathy (Mainly in Cervical Region)
            - Subsequent signs depends on infiltration of other body systems.
        - **Diagnosis:**
            - Physical Exam
            - Blood Tests
            - Bone Marrow Test
            - CT-scans
            - Lymph node Biopsy
        - **Treatment:**
            - Chemotherapy

Multiple Myeloma:

- **Characterized By:**
  - Proliferation of ***Plasma Cells*** in the bone marrow
  - → Overproduction of Immunoglobulins
- **Clinical Signs:**
  - Often Asymptomatic
  - However:
    - Excess Immunoglobulins → Blocks + Damages Renal Tubules
    - Excess Immunoglobulins → Lyses Bone → Bone Pain
      - Bone Lysis → Anaemia → Lethargy.
      - Bone Lysis → Elevate Blood-Ca^{+}
- **Diagnosis:**
  - protein electrophoresis of the blood and urine → For Presence of 'Paraprotein' (an Abnormal Immunoglobulin produced by Tumor Plasma Cells)
  - A bone marrow biopsy is usually performed to estimate the percentage of bone marrow occupied by plasma cells.
- **Treatment:**
  - Chemotherapy
  - Stem-Cell Transplantation

Myelodysplastic Syndromes (AKA "Pre-Leukaemia"):

- Diverse Group of Haematological Conditions:
- **Characterised By:**
  - *Ineffective Production* (Dysplasia) of Myeloid Blood Cells
- **Most Common in Elderly**
  - 60-75
- **Clinical Signs:**
  - **Bone-Marrow Failure → Abnormalities of All 3 Myeloid Cell Lines:**
    - ↓RBCs → Anaemia
    - ↓Granulocytes → Neutropaenia
    - ↓Platelets → Thrombocytopaenia
  - **Often leads to Acute Myeloid Leukaemia**
- **Diagnosis:**
  - Excessive Bruising/Bleeding
  - Infections
  - Abnormal RBCs
  - Abnormal WBCs
  - Chromosome Abnormalities
- **Treatment:**
  - Chemotherapy

Leukaemias

What Are Leukaemias?:

- **= Myeloproliferative & Lymphoproliferative Disorders**
- ***=A Type of Cancer*** *Caused by Unregulated Proliferation of Abnormal 'White Cells' from a* ***Mutant*** *Haematopoietic Stem Cell.*
- **Mutation** – Genetic Alteration within a *Single Myeloid (Bone Marrow)OR Lymphoid Tissue.*
    - **Chromosomal Translocations:**
        - ***Philadelphia Chromosome:**
            - *#1 Cause of:* → *Chronic Myeloid Leukaemia
    - **Chromosomal Deletions/Additions:**
        - ***Monosomy 7:**
            - *#1 Cause of:* → *Acute Myeloid Leukaemia
    - **Point Mutations**
    - **Gene Amplification:**
        - **Changes in Proto/Anti-Oncogenes:**
            - Oncogenes: Code for proteins involved in cell proliferation/differentiation.
            - Abnormal Proto/Anti-Oncogenes → Cancers (ie. Leukaemia)
            - Eg. A Hypermorphic Mutation in an *Oncogene* → Hyperactive Proliferation
            - Eg. A Hypomorphic Mutation in a *Tumour-Suppressve* Gene → Hyperactive Proliferation

Classification of Leukaemia:

- **Acute:**
    - **Myeloid:**
        - Acute Myeloid Leukaemia:
    - **Lymphoid:**
        - Acute Lymphoblastic Leukaemia
- **Chronic:**
    - **Myeloid:**
        - Chronic Myeloid Leukaemia
    - **Lymphoid:**
        - Chronic Lymphocytic Leukaemia
- **Other:**
    - **Hairy-Cell Leukaemia**
    - **Prolymphocytic Leukaemia**
    - **T-Cell Leukaemic Lymphoma**

Acute Myeloid Leukaemia:

- **Characterised By:**
  - Rapid proliferation of *Malignant Cells* → Accumulate in the bone marrow
- **Most Common in ADULTS** –↑Incidence with Age
- **Subdivided in 8 Types** – Defined by **"FAB-Scheme"** (French/American/British)
  - Based on the *Type of Cell* from which the leukaemia developed + Maturity
  - 8 Groups = 'M0' → 'M7'
- **Clinical Signs:**
  - **Anaemia – Low [Hb] (due to ↓RBCs)**
    - Fatigue
    - Shortness of Breath
  - **Neutropaenia – (Low Neutrophils)**
    - ↑Malignant White Blood Cells + ↓Normal White Blood Cells
    - Susceptible to Infection
  - **Thrombocytopaenia – (Low Platelets)**
    - Easy Bruising/Bleeding
- **Reasons for Clinical Signs:**
  - Rapid proliferation of *Malignant Cells* → Accumulate in the bone marrow
    - → 'Packs Out' the bone→ interfere with the production of normal blood cells
  - Hence, Symptoms Caused by **Replacement of Normal Bone Marrow with Leukaemic Cells**
    - → **↓RBCs**
    - → **↓*Normal* White Blood Cells**
    - → **↓Platelets**
- **Diagnosis:**
  - **Complete Blood Count:**
    - Excess Abnormal Leukocytes
    - Blast Cells (Big, Immature Cells)
    - Anaemia
    - Thrombocytopaenia
  - **Bone Marrow Aspiration/Biopsy:**
    - Required for *Definitive* Diagnosis
    - Presence of Blast Cells
  - **Cytogenetics:**
    - Testing for Chromosomal Translocations
  - **Cytochemistry:**
    - Using *Cytochemical Stains* to Differentiate between AML & ALL
      - Stains = Myeloperoxidase & Sudan Black Stain
        - AML – Positive with Both Stains.
        - ALL – Negative with Both Stains.
- **Treatment:**
  - **Chemotherapy**
  - **Haematopoietic Stem Cell Transplant**

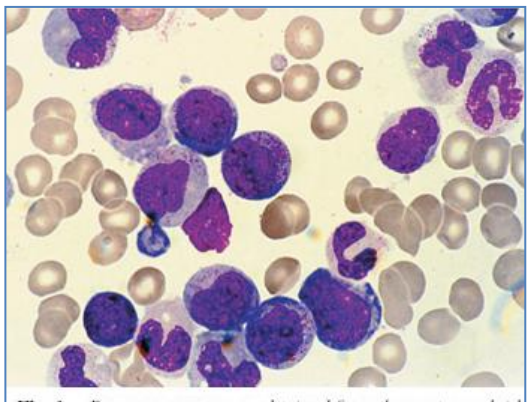
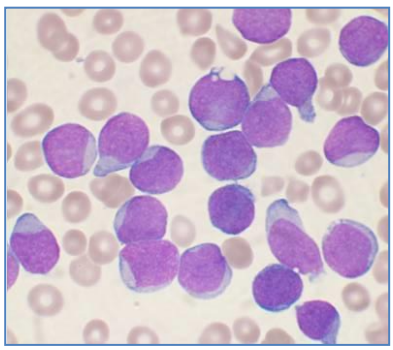


Fig. 1 – Bone marrow smear obtained from the acute myeloid leukaemia subtype M2 case at diagnosis showing blast cells, promyelocytes, myelocytes and neutrophils (Romanovsky, 100x)

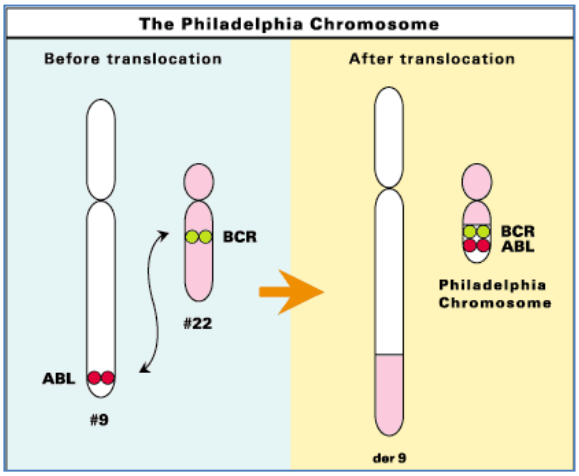
Acute Lymphoblastic Leukaemia:

- **Characterised By:**
  - Excess B-Lymphoblasts. (B-Lymphocyte Precursors)
  - Malignant, immature white blood cells continuously multiplying in the bone marrow.
  - A.L.L. crowds out normal cells in the bone marrow, and spreads (metastases) to other organs.
  - Can be fatal in weeks to months if left untreated.
- **Most Common in CHILDREN** ('Children's Leukaemia')
  - Peak incidence at 4-5 years of age
- **Subdivided Based on:**
  - Morphology
  - Cell-Surface Antigens
- **Clinical Signs:**
  - **Anaemia – Low [Hb] (due to ↓RBCs)**
    - Fatigue
    - Shortness of Breath
  - **Thrombocytopaenia – (Low Platelets)**
    - Easy Bruising/Bleeding
  - **Frequent Fevers/Infections**
  - **Weight-Loss/Loss of Appetite**
  - **Bone/Joint Pain**
  - **Enlarged Lymph Nodes**
  - **Enlarged Liver/Spleen**
  - **Oedema in Lower Limbs**
- **Reasons for Clinical Signs:**
  - Lack of normal and healthy blood cells due to crowding out by malignant and immature WBC's.
  - Therefore, symptoms due to malfunctioning of:
    - Red Blood Cells
    - Leukocytes
    - Platelets
- **Diagnosis:**
  - **Physical Examination**
  - **Complete Blood Count:**
    - Excess Abnormal Leukocytes
    - Blast Cells (Big, Immature Cells)
    - Anaemia
    - Thrombocytopaenia
  - **Bone Marrow Aspiration/Biopsy:**
    - Required for *Definitive* Diagnosis
    - Presence of Blast Cells
  - **Cytogenetics:**
    - Testing for Chromosomal Translocations
      - Particularly for the 'Philadelphia Chromosome'
  - **Cytochemistry:**
    - Using *Cytochemical Stains* to Differentiate between AML & ALL
      - Stains = Myeloperoxidase & Sudan Black Stain
        - AML – Positive with Both Stains.
        - ALL – Negative with Both Stains.
- **Treatment:**
  - **Chemotherapy**
  - **Radiotherapy**



Chronic Myeloid Leukaemia:

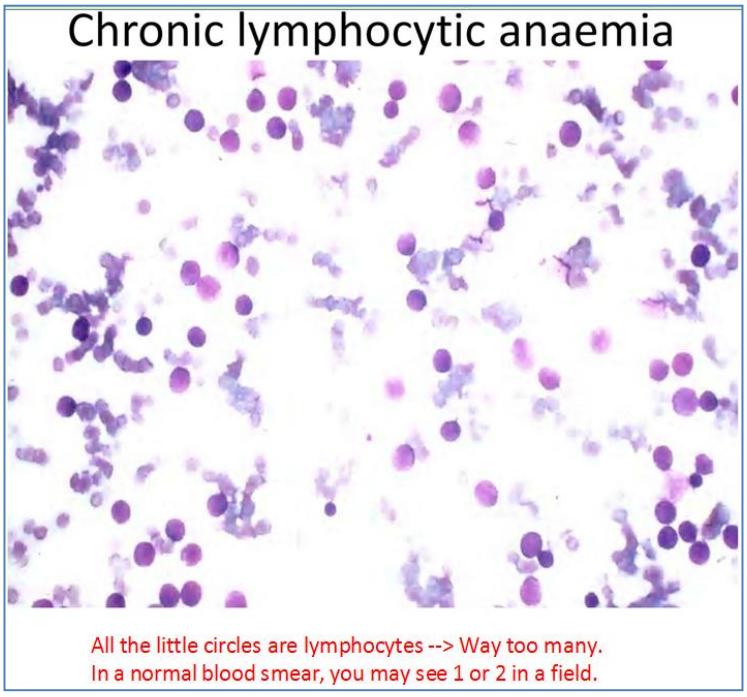
- **Characterized By:**
  - - A characteristic chromosomal translocation called the Philadelphia chromosome. →
    - High, Unregulated growth of myeloid cells in the bone marrow →accumulation in the blood.
    - ↑↑Proliferation of Mature & Immature Granulocytes (neutrophils/eosinophils/basophils).
- **Most Common in ADULTS:**
  - Peak incidence (50-60yrs)
- **Clinical Signs:**
  - **Often Asymptomatic** (Usually detected by routine blood tests)
  - **Anaemia – Low [Hb] (due to ↓RBCs)**
    - Fatigue
    - Shortness of Breath
  - **Thrombocytopaenia – (Low Platelets)**
    - Easy Bruising/Bleeding
  - **Malaise** (general feeling of being unwell)
  - **Mild Fever**
  - **Gout** (Metabolic Arthritis – Due to ↑[Uric Acid] in blood)
- **Phases:**
  - **Chronic Phase:**
    - See above for symptoms
  - **Accelerated Phase:**
    - Progression of CML → can change to an Acute Form
    - 'Blast Crisis' is imminent.
  - **Blast Crisis:**
    - Fatal Acute Leukaemic Phase
    - Final phase in the evolution of CML
    - Behaves like an acute leukaemia
    - Rapid Progression + Short survival.
    - Requires Immediate Bone Marrow Transplant to Survive.
- **Diagnosis:**
  - **Ultimately by Detecting the 'Philadelphia Chromosome'**
    - Via Cytogenetics (Testing for Chromosomal Translocations)
  - **Bone Marrow Aspiration/Biopsy:**
    - Presence of Blast Cells
    - Not enough to diagnose.
- **Treatment:**
  - **Chronic Phase:**
    - Tyrosine Kinase Inhibitors
  - **Blast Crisis:**
    - Requires Immediate Bone Marrow Transplant to Survive.



Results when part of Ch.9 switches places with part of Ch.22. Forms an extra-long Ch.9, & an extra-short Ch.22 = The Philadelphia Chromosome. – Contains the abnormal gene-fusion.

Chronic Lymphocytic Leukaemia:

- **Characterized By:**
  - Overproliferation of Mutated B-Cells → Can't Fight Infection.
  - The cells accumulate mainly in the bone marrow and blood.
- **Most Common in ADULT MALES:**
  - Peak incidence (50-60yrs)
- **Clinical Signs:**
  - Most diagnosed without symptoms via routine blood test →returns high white cell count
  - Advances To:
    - Swollen lymph nodes
    - Splenomegaly
    - Hepatomaegaly
    - Eventually Anaemia and Infections.
- **Diagnosis:**
  - Most diagnosed without symptoms via routine blood test →returns high white cell count
    - CLL is usually first suspected by the presence of a lymphocytosis, an increase in one type of the white blood cell, on a complete blood count (CBC) test.
- **Treatment:**
  - Early CLL is not treated
  - CLL treatment is only taken when clinical symptoms/blood counts indicate progression to a point where it may affect the patient's quality of life.
  - Late CLL is treated with chemotherapy and monoclonal antibodies.



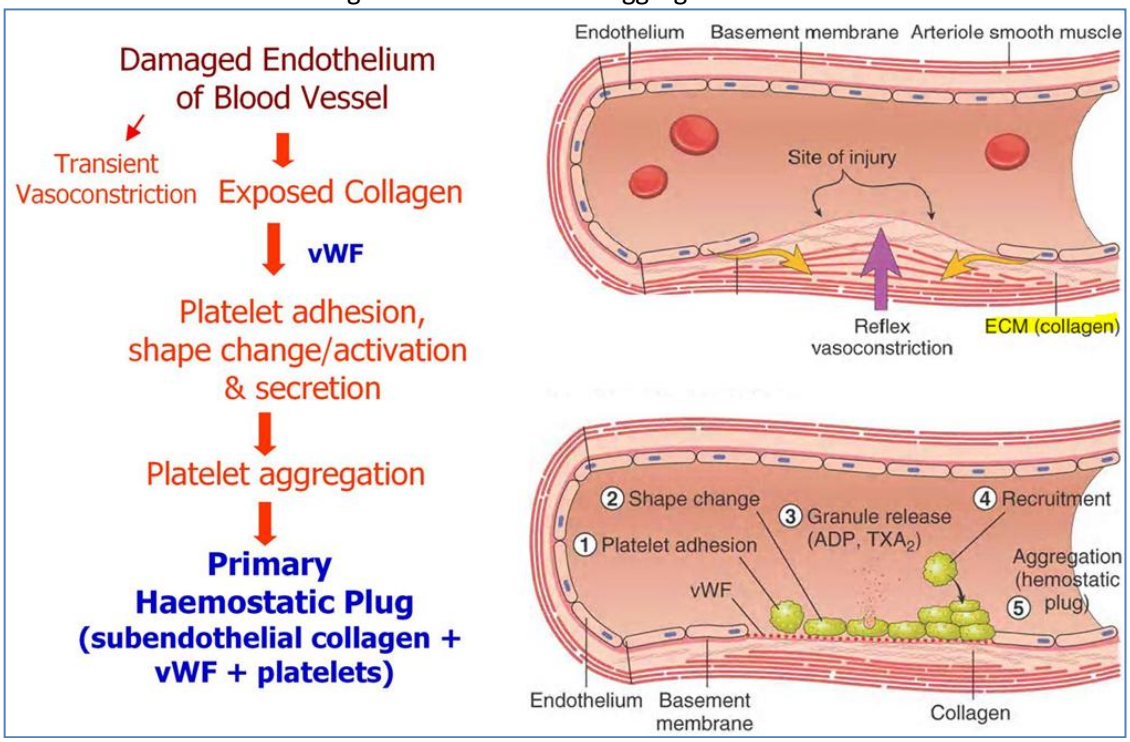
Haemostasis:

- **1. Primary Haemostasis:**
  - **Vascular Spasms:**
    - Vasoconstriction: The immediate response to vessel damage.
  - **Primary Platelet Plug Formation:**
    - Platelets form a 'plug' → *Temporarily* seals the break in vessel wall
    - When vessel is damaged → ***Sub-Endothelial Collagen*** is exposed....
      - Platelets ***(+ Von Willebrand Factor*** [glue]***)*** adhere strongly to the Collagen Fibres...
      - Primary Platelet-Plug 'Sandwich':

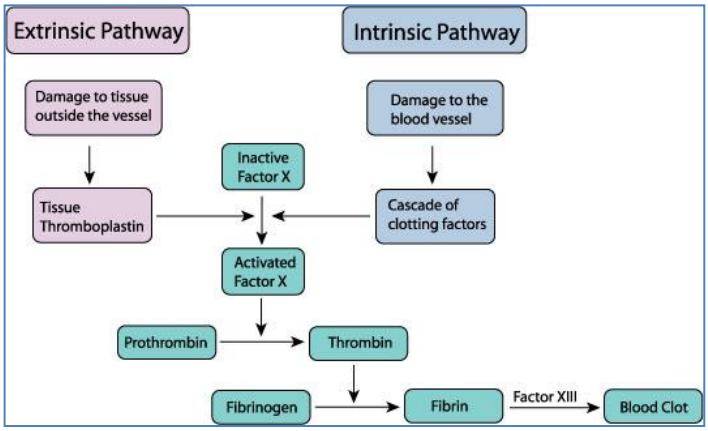
        Surface Glycoproteins on Platelets

        Von Willebrand Factor

        Sub-Endothelial Collagen
  - **Platelet Aggregation:**
    - Once attached, Platelets → Activated → ***Release Several Chemicals:***
      (Platelet Activation & Secretion Enhanced by Thrombin)
      - **Serotonin:** Vasoconstrictor
      - **ADP:** Potent Platelet-Aggregating Agent
      - **Calcium (Factor IV):** A cofactor that *Activates* other *Inactive Pro-Coagulation Factors*.
        :. Important in Coagulation
      - **Thromboxane A_2:** Vasoconstrictor
        Potent Platelet-Aggregating Agent
    - Initiates a Positive Feedback Cycle → Activates & Attracts more & more Platelets.
      - Within 1min, a platelet plug is built → further reduces blood loss.
  - **Platelet-Plug Localisation:**
    - **Prostacyclin:**
      - A Prostaglandin Produced by *Intact* Endothelial Cells.
      - A Strong *Inhibitor* of Platelet Aggregation



- **2. Secondary Haemostasis:**
  - **Coagulation Cascade:**
    - Coagulation (i.e. Blood 'Clotting'): Where Blood; Liquid → Gel
    - Series of enzymatic conversions of *Inactive Coag. Factors* → *Active Coag. Factors.*
    - **Intrinsic Pathway:**
      - →**Triggered by Exposed Sub-Endothelial Collagen**
      - All factors needed for clotting are in the blood
    - **Extrinsic Pathway:**
      - →**Triggered by Exposed Tissue Factor** (Factor III)



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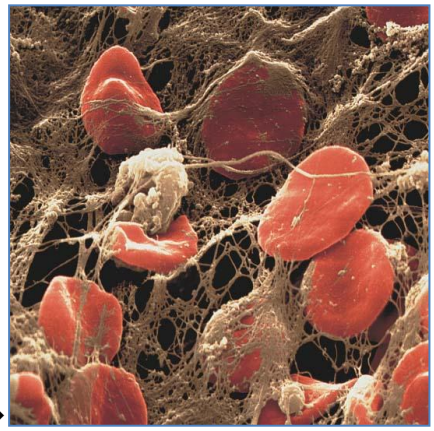


    - Both Pathways eventually lead to ***Activation of Factor-X***
      - **1. Activated Factor-X** combines with other factors→
      - **2. Prothrombin Activator** is formed...
      - **3. Prothrombin Activator**; converts the plasma-protein: ***Prothrombin → Thrombin*.**
  - **Fibrin Deposition:**
    - **4. Thrombin** Catalyses Conversion & Deposition of ***Fibrinogen →Fibrin***
      - Also **+Ve Feedback** on Coag. Cascade (Amplification of ProThrombin Activation)
    - **5. Fibrin** Mesh →+ ***Active Factor-XIII*** → Stabilises the Platelet-Plug → Seals the hole
      - **Primary Platelet Plug** + *Mesh* → **Secondary Platelet Plug.**
  - **Coagulation Localisation:**
    - **Anticoagulants:** See Above
      - **Tissue Factor Pathway Inhibitor:**
        - Inactivates Factor-X_a
        - Inhibits [Factor-VII_a – Tissue Factor Complex]
      - **Thrombomodulin:**
        - Binds Thrombin – Fibrinogen can't convert to Fibrin
      - **Protein C & Protein S:**
        - Combine to *Inactivate Factor-V_a & Factor-$VIII_a$*.
      - **Antithrombin *(+ Heparin)*:**
        - Inhibits Thrombin
        - Inhibits Factor-X_a & Factor-XI_a

- **3. Fibrinolysis:**
  - Clots aren't permanent solutions to vessel injuries.
  - :. Fibrinolysis removes un-needed clots after healing has occurred...by:
  - **Blocking Coagulation Cascade:**
    - **Thrombomodulin:**
      - Blocks Thrombin from activating Fibrinogen :. No Fibrin Deposition
  - **& By Breaking Down Fibrin:**
    - Via a *Fibrin-Digesting Enzyme:* ***Plasmin*** → Degrades fibrin & :. The clot as well.
      - Plasmin: Produced when ***Plasminogen*** is activated.
      - **Plasminogen Activation:** (once clot is formed)
        - **Endothelial Cells:** secrete ***Tissue Plasminogen Activator (tPA)***
        - **Activated Factor XII:** also *Activates Plasminogen*
        - **Thrombin:** also *Activates Plasminogen*

Disorders of Haemostasis

Bleeding Disorders:

- **Thrombocytopenia, Defective Platelet Function & Von Willebrand's Deficiency:**
  - **Thrombocytopenia:**
    - Due to ***deficient number of platelets.***
    - Results from either:
      - ↓ Platelet Production
      - ↑ Platelet Destruction
      - ↑ Platelet Consumption (in large injuries/burns)
  - **Defective Platelet Function:**
    - There are enough platelets, but not working properly.
    - May be Inherited (rare)...OR
    - Acquired: (eg. From Aspirin/other blood thinners)
  - **Von Willebrand's Deficiency:**
    - Due to Either:
      - Not enough vWF....or
      - Dysfunction of vWF.
    - Ordinarily vWF is necessary for platelet adhesion.
    - :. Deficiency → Poor platelet plug formation
- **Coagulopathy = Defective Coagulation:**
  - Bleeding disorders
    - **Heriditary:**
      - **Haemophilia A: Factor VIII Deficiency:**
        - Most common
        - Sex Linked Recessive (Female Carriers; Affected Males)
      - **Haemophilia B: Factor IX Deficiency:**
        - AKA. Christmas Disease
        - Less common
        - Sex Linked Recessive (only affects males)
      - **Other deficiencies (Factors V, VII, X, XI & XIII) Rare.**
        - Just know they exist.
    - **Acquired:**
      - **Vitamin K Deficiency (Factors II, VII, IX, X)**
        - Due to either:
          - Diet
          - Malabsorption
          - Long-term warfarin
      - **Liver Disease:**
        - Eg. Billiary Obstruction:
          - Hinders absorption of Fat-Soluble vitamins
          - Reduced synthesis of Factors II, VII, IX & X
        - Eg. Severe Hepatocellular Damage:
          - Reduced synthesis of Factor V & Fibrinogen
      - **DIC - Disseminated Intravascular Coagulation:**
        - AKA. Consumptive Coagulopathy
        - Formation of small clots inside blood vessels throughout the body.
        - Leads to: ↑Consumption of Platelets & Coagulation Factors.

Thrombotic Disorders:

- Can cause obstruction to flow → Ischaemia → Necrosis
- **Can Move Elsewhere = "*ThromboEmbolism":***

- **Arterial Thrombosis:**
  - **Atherosclerotic Plaque in Arterial walls → Arterial Thrombosis.**
    - Ie. Rupture of Atherosclerotic Plaque →
      - Exposure of SubEndothelial Collagen
      - Exposure of Tissue Factor
  - **Most common cause of:**
    - **CerebroVascular Accidents (CVA's)** – aka. Stroke – Clot in brain → Necrosis of Neurons
    - **Myocardial Infarction (MI)** – Due to Thrombi related to atherosclerosis in Coronary Arteries → Necrosis of Myocardium
    - **Peripheral Arterial Disease (PAD)**
- **Venous Thrombosis:**
  - Very Rare (Affects 1/1000 people)
  - Occur Mostly in Lower Extremities (due to gravity pooling blood)
    - Patient may present with sore or swollen legs/calves.
    - **Acquired Hypercoagulable States:**
      - **High-Dose Oestrogen Therapy:**
        - ↑Plasma levels of Coag. Factors
        - ↓ Antithrombin & Tissue-Plasminogen-Activator
      - **Major Surgery/Trauma:**
        - Due to high tissue damage
        - Immobility after surgery (Venous Stasis)
        - Exposure of Tissue Factor
      - **Pregnancy & Post-Partum (↑Levels of Coag. Factors during pregnancy)**
      - **Sepsis (bacterial infection → widespread damage to endothelium)**
      - **Heparin-Induced Thrombocytopaenia** (some people on heparin develop antibodies to their own platelets)
      - **Blood Stasis**:.....from:
        - Heart Failure (not pumping adequately)
        - Stroke
        - Prolonged Immobility
        - Nephrotic Syndrome (loss of Coag. Factors through Urine)
        - Varicose Veins

Evaluation of Haemostasis:

- **Platelet Count**
  - Literally the number of platelets/volume of blood.
  - Normal range = 150-400x10^9/L
  - Excessively Low platelet count → Thrombocytopenia (bleeding disorder)
- **Tests of Coagulation-Factor Function:**
  - **Prothrombin Time (PT):**
    - *Time taken for plasma to clot after addition of tissue factor (Factor III)*
    - Measures *Extrinsic Pathway* + part of *Common Pathway*
    - Measures factors VII, X, V, II (Prothrombin) and I (fibrinogen).
    - Normally 12-15sec.
    - 15sec+ = One/more of above factors are deficient.
    - INR (International Normalized Ratio) is derived from PT → Universal measurement.
  - **Activated Partial Thromboplastin Time (aPTT):**
    - *Time taken for plasma to clot after addition of phospholipids*
    - Measures *Intrinsic Pathway* + the *Common Pathway*
    - Measures factors XII, XI, IX, VIII, X, V, II (Prothrombin) and I (fibrinogen).
    - Normally 25-45sec.
    - 45sec+ = One/more of above factors are deficient.
  - **Thrombin Time:**
    - Measures how quickly Thrombin is being activated.
    - Time taken for a clot to form, following addition of animal Thrombin.
    - Measures:
      - The conversion of Fibrinogen → Fibrin.
      - Any deficiency of fibrinogen
      - Any inhibition of thrombin.

Evaluation of Thrombosis:

- **Prothrombin Time (PT):**
  - *Time taken for plasma to clot after addition of tissue factor (Factor III)*
  - *Detects deficiency of Factor VII*
- **Activated Partial Thromboplastin Time (aPTT):**
  - *Time taken for plasma to clot after addition of phospholipids*
  - *Detects deficiency of Factors VIII, IX, XI or XII.*
- **If *Both* PT & aPTT are Abnormal:**
  - *Probably due to:*
    - *Liver disease*
    - *Vit. K Deficiency……..or*
    - *Oral Anticoagulants*

The Main 2 AntiCoagulant Drugs:

- **Heparin (INJECTABLE):**
  - Fast-acting
  - How?: Stimulates Antithrombin Activity
    - Standard Heparin:
      - Rapid Action
      - Initially administered by IV, then SubCutaneously.
    - Low Molecular-Weight Heparin:
      - Slower Action
      - But Longer Half-Life
- **Warfarin (ORAL):**
  - Most common oral Coag.
  - How?: Vitamin K Antagonist (Decreases Factors II, VII, IX & X)

Fibrinolytic Drugs:

- Degrade Thrombi
- Used Systemically...or...injected directly into thrombus.

Antiplatelet Drugs:

- Eg. Aspirin:
  - Reduces Thromboxane A_2 Production
  - Reduces Platelet Aggregation
  - Often used in patients with Atherosclerosis → Prevents Thrombi.

Blood Products:

- **--Whole Blood:**
  - Cells/Platelets
  - Plasma
  - **Reason For Transfusion:**
    - Acute Blood Loss
- **Red Blood Cells:**
  - RBC's
  - **Reasons for Transfusion of RBCs:**
    - **Mainly to *Quickly improve O_2 Delivery to Tissues.***
      - Expect a rise of *10g/L* of Haemoglobin *Per Unit of Blood (450mL)*
    - **Egs of Eligable Recipients:**
      - Acute Blood Loss
      - Preoperative
      - Anaemias
      - Renal failure
      - Bone Marrow Failure
      - Septicaemia
      - Haemolytic Disease of the Newborn.
- **Granulocyte Concentrates:**
  - White Blood Cells (leukocytes)
  - **Reason For Transfusion:**
    - Supportive Therapy for Neutropenia (Low White Cell Count)
    - Eg. Pts following radiotherapy.
- **Platelet Concentrate:**
  - Platelets
  - **Reasons For Transfusion:**
    - Severe Thrombocytopenia
    - Severe Bone-Marrow Failure (Ie. Acute Leukaemia)
    - Myelotoxic Chemotherapy
- **--Plasma:**
  - Blood proteins
  - Clotting Factors
  - **Reasons For Transfusion:**
    - Replacement of Coagulation Factors
    - Eg. Haemophilia & other Bleeding Disorders.
- **Cryoprecipitate:**
  - Clotting Factors
  - Fibrinogen
  - **Reasons For Transfusion:**
    - Used To Control Clotting Disorders.
    - **Factor VIII & Fibrinogen:**
      - Treatment of Haemophilia
    - **Factor IX & Prothrombin:**
      - Treatment of Factor IX Deficiency
      - Treatment of Christmas Disease.
- **Cryosupernatant:**
  - Albumin
  - Immunoglobulins
  - **Reasons For Transfusion:**
    - Used as 'Volume Expanders' – in Hypovolumic Shock
    - **Albumin:**
      - Volume Expander
      - To Treat HypoAlbuminaemia – eg. Burns/Renal Patients.
    - **Immunoblobulins:**
      - Treatment of Immunocompromised Patients

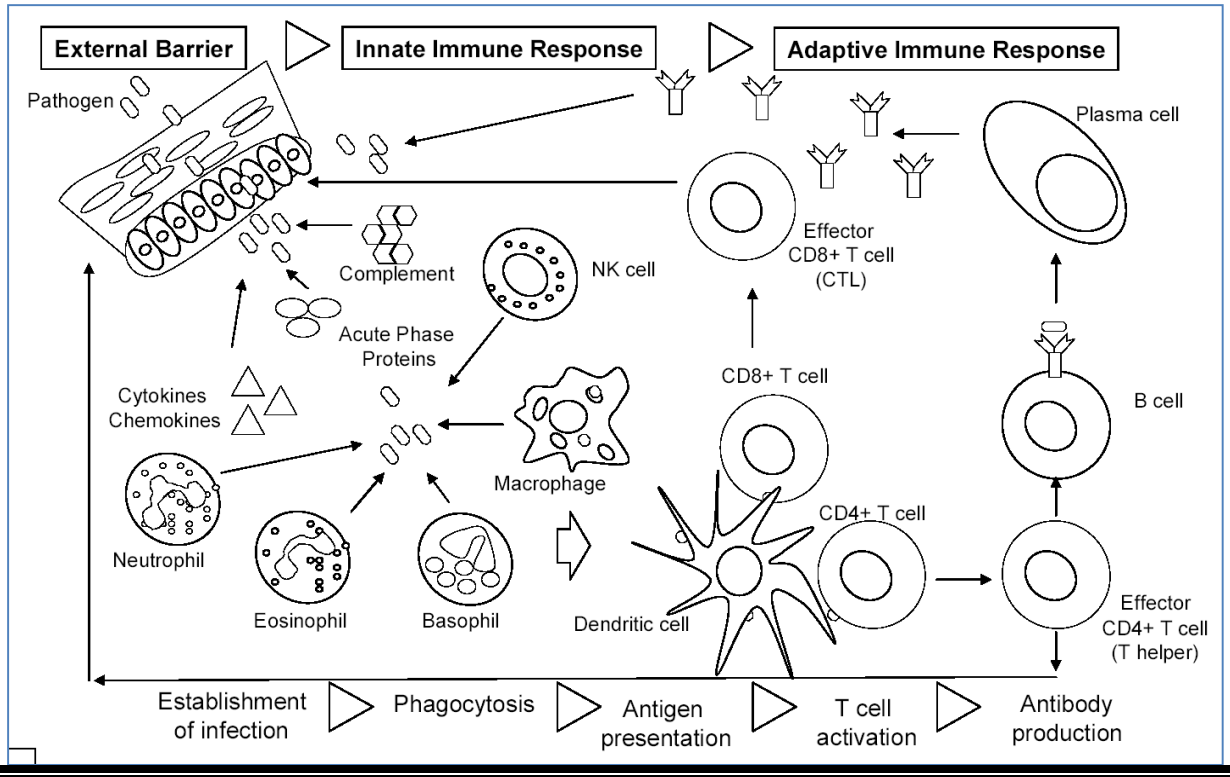
The Immune System – At A Glance

The Immune System:

- The immune system is more a ***functional*** **system rather than an** ***anatomical*** **or** ***organ-based*** system.
- Consists of:
  - a diverse array of molecules
  - -and trillions of immune cells (especially lymphocytes).
    - These molecules & immune cells inhabit lymphoid tissues & circulate in body fluids.
- Functions to protect the body from:
  - Most infectious microorganisms
  - Cancer cells
  - Transplanted organs
  - Grafts
  - Any other foreign material
- Can act directly – by cell attack
- Can act indirectly – by releasing mobilising chemicals & antibody molecules.

Terminology:

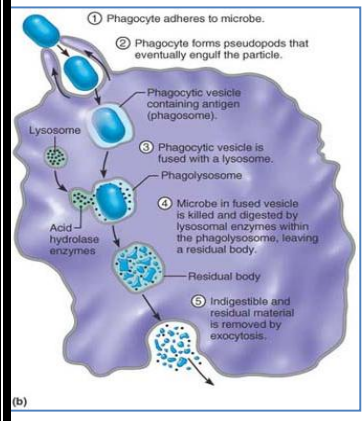
- **Pathogen:** microorganism that is able to cause disease
- **Pathogenicity:** the ability of a microorganism to cause disease.
- **Virulence:** the degree of pathogenicity.
- **Opportunistic pathogens:** bacteria which cause disease in a compromised host.
- **Normal flora:** harmless bacteria consistently associated with the host.
- **Infection:** when an organism (incl. Normal flora) breaches a body surface.
  - Doesn't necessarily lead to disease
    - Depends on:
      - Route of entry
      - Number of pathogens
      - Immune status of host



Defence Systems of the Body:

- **Innate (**non-specific**) Immune System:**

- *"the body's foot-soldiers"*
- Already in place at birth.
- Is always prepared
- Responds within minutes
- Protects the body from all foreign substances.
- Are often sufficient to ward off invading pathogens single-handedly.
- Essentially, it reduces the workload of the adaptive system.
- The body's first 2 lines of defence.
    - **1st Line of Defence: Surface Barriers:**
        - **Prevents Entry of Pathogen**
            - Skin
                - Stratified
                - Heavily keratinised
            - Mucous membranes
                - Lysozyme: enzyme found in saliva & tears →destroy bacteria.
                - Sticky Mucus: in digestive & respiratory tracts →traps bacteria.
                - Cilia – nasal & respiratory →sweep bacteria into mouth→swallowed.
                - Acid secretion: skin, vagina, stomach →kills microbes.
    - **2nd Line of Defence: Internal Defenses:**
        - **Prevents Spread of Pathogen If Surface Barriers are Breached**

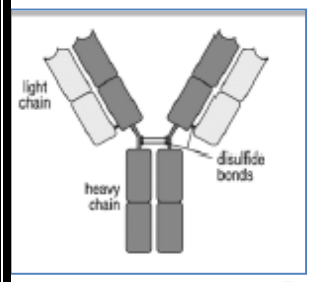


- **Phagocytes**
    - **Macrophages** – Large phagocytic cells
- **Granulocytes –** possess cytoplasmic granules
    - **Neutrophils** –they release toxic chemicals into the extracellular fluid, killing both the target and themselves. (kamikaze)
    - **Eosinophils** – another type of white blood cell – **kill parasitic worms**.
    - **Basophils** – important in allergic reactions
- **Fever**
    - When exposed to foreigners, leukocytes & macrophages secrete pyrogens → increases the body's thermostat.
    - Increases metabolic rate, kills microbes, speeds up repair.
- **Natural Killer cells**
    - Police the body in blood & lymph
    - Can lyse & kill cancer cells & virus-infected cells
    - Target all cells that lack 'self' surface receptors (non-specific)
    - Kill by latching onto invaders and inducing apoptosis.
    - Also secrete potent chemicals that promote inflammation
- **Antimicrobial proteins**
    - Either attack microbes directly or reduce their reproductive ability.
    - –'Interferons' & 'compliment'
- **Inflammation**
    - In response to physical trauma/intense heat/bad chemicals/infection.
    - Prevents spread of damaging agents to nearby tissue
    - Disposes of cell debris & pathogens
    - Sets stage for repair.
    - Characterised by **heat, redness, pain & swelling**

- **Adaptive (**specific**)Immune System:**

- "The body's elite special forces" – equipped with high-tech weapons.
- Adaptive responses are called into action as 'reinforcements'
- Takes much more time to mobilise than the innate response.
- Attack specific foreign substances – incl. Antigens and abnormal body cells
- When disabled → cancer, AIDS, etc.
- Tremendously amplifies the inflammatory response.
- **>It is Specific:** recognises *particular* pathogens/antigens
- **>It is Systemic:** immunity isn't restricted to initial infection site
- **>It has Memory:** mounts stronger attacks on previously encountered pathogens.
-

  - **The body's 3rd line of defence**
    - **Humoral Immunity** (aka. Antibody-mediated immunity)



-Immunity can be **transferred** from person-person **via serum**

- **B Cells (B-Lymphocytes)**
  - **Make antibodies** against soluble antigens.
- **Antibodies (Immunoglobulins):**
  - Circulate freely in blood & lymph
  - **Neutralises** bacteria/toxins/& viruses →marks for destruction by phagocytes or compliment.

    - **Cellular Immunity**

-Immunity can be **transferred** from person-person **via blood cells**

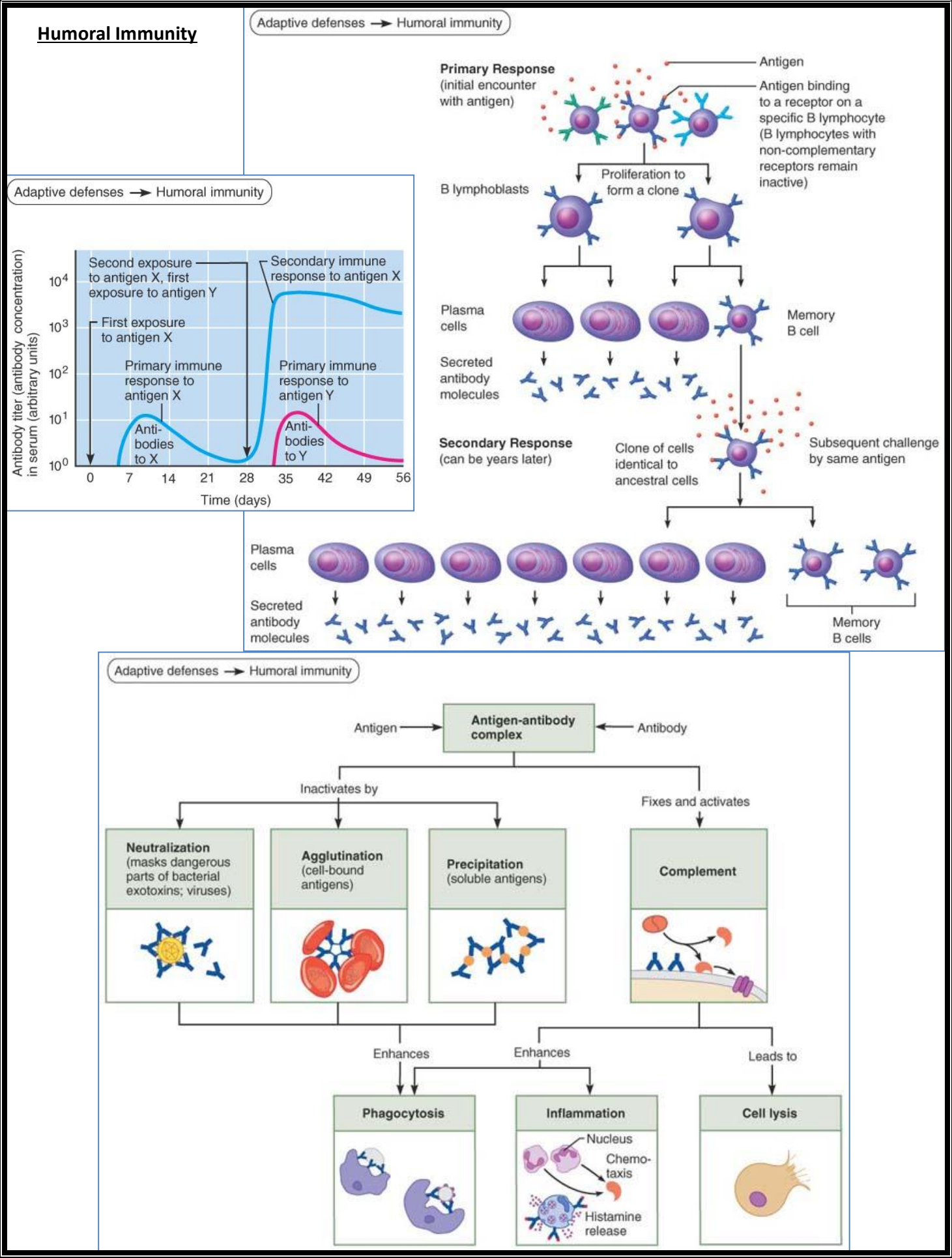
- Antigen **causes activation of** macrophages, NK-cells, T-lymphocytes & cytokines
  - Macrophages & NK-Cells – destroy intracellular pathogens
  - **T Cells (T-Lymphocytes)** – induce apoptosis of body cells with viruses/intracellular bacteria/cancerous traits.
  - Cytokines are secreted – enhance inflammatory response and/or activate other lymphocytes/macrophages.
- Activated cells **destroy** infected/foreign cells.

Summary

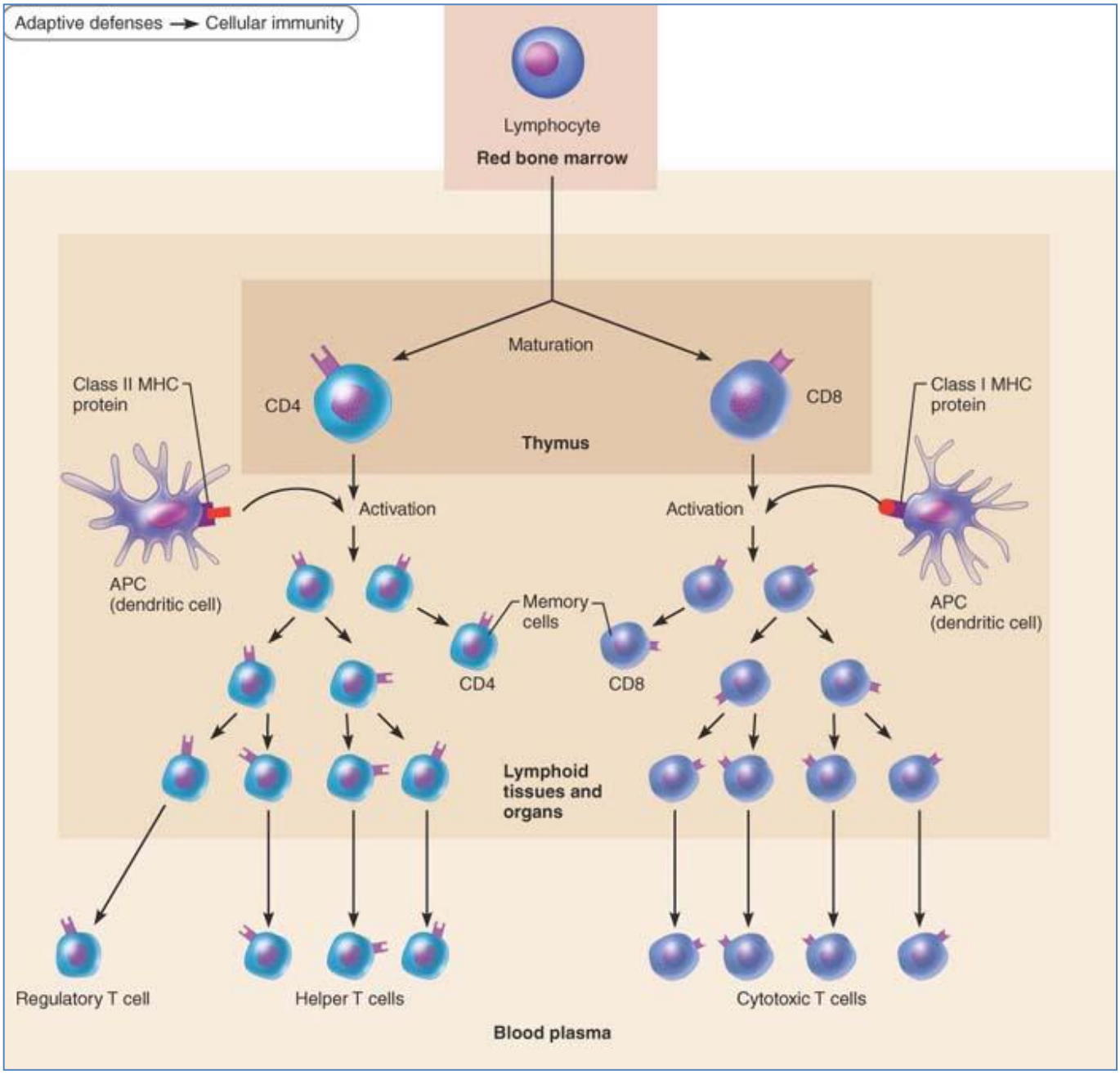
INNATE Vs ADAPTIVE IMMUNITY

	Innate	Adaptive
Barriers	skin, epithelia, chemicals	epithelial Lϕ, Ab secretion
Proteins	complement system	antibodies
Cells	phagocytes and NK cells	lymphocytes
Specificity	shared structures of microbes	antigens
Diversity	low	very high
Memory	nil	+
Tolerance	+	+

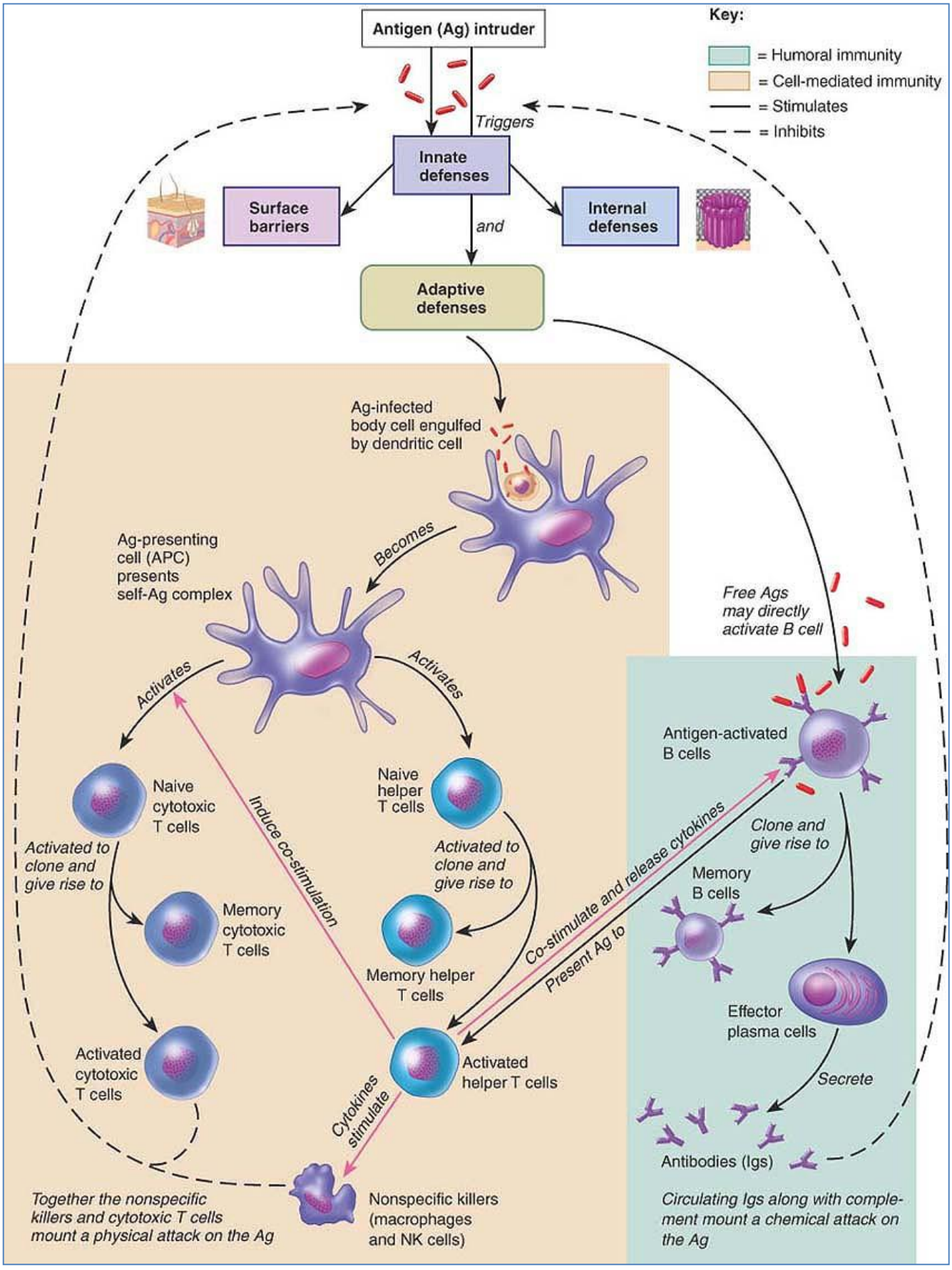
Humoral Immunity



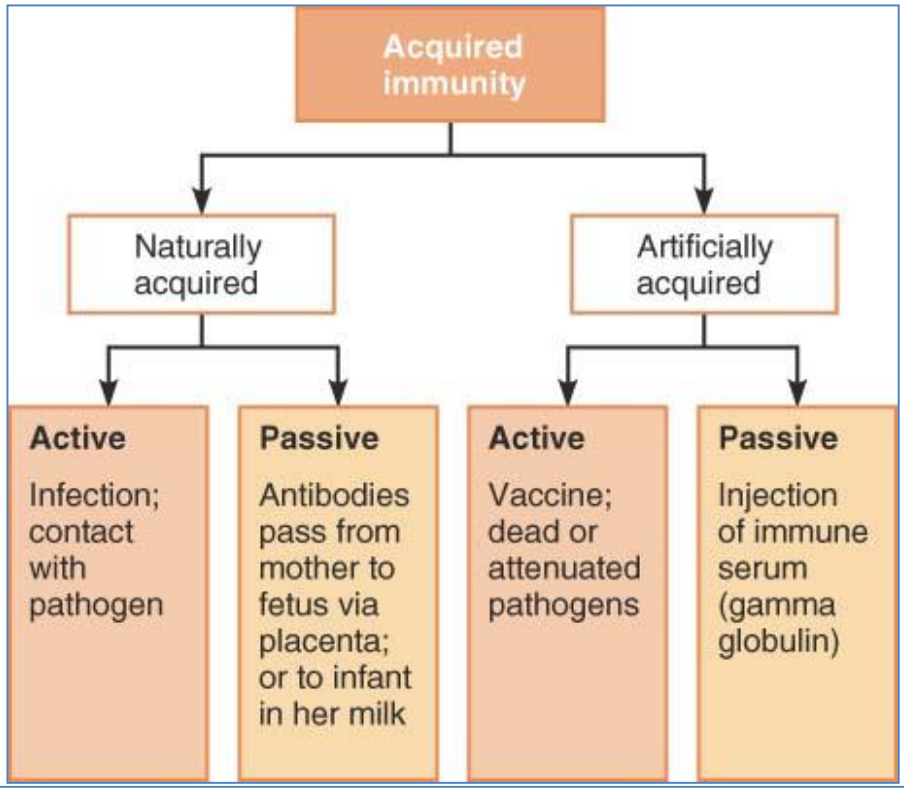
Cellular Immunity:

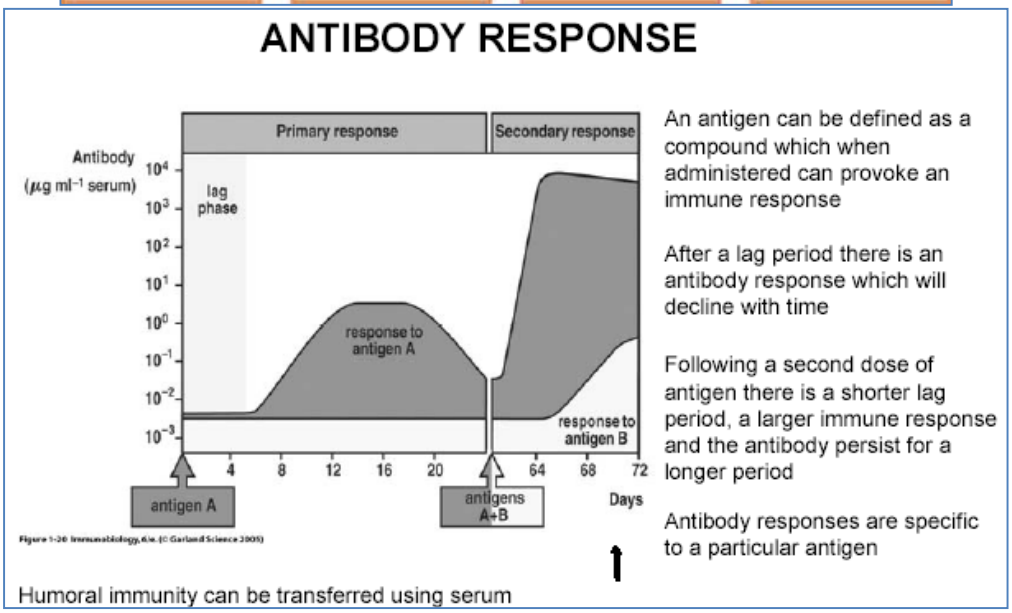


The Whole Immune System Summary:



- **Vaccination**
  - **Whole organism vaccines**
    - Effective against complex pathogens (viruses & bacteria)
  - **Live Attenuated vaccines**
    - Live organisms that have been de-pathogenised
  - **Inactivated/killed vaccines**
    - Dead organisms containing relevant proteins but unable to replicate
  - **Recombinant vaccines**
    - Artificially synthesised non-toxic antigens.





Haematopoiesis

Haematopoiesis:

- 'The Formation of Cells in the Blood'
- Foetal Life: Takes place in the Yolk Sac/Liver/Spleen/&Bone Marrow.
- Childhood→Adult: Takes place only in the **Bone Marrow** (Medullary Cavity)
    - Ie. The Bone Marrow is the only source of *new blood cells*.
        - Adults: Haematopoiesis confined to axial skeleton & proximal ends of Femur & Humerus.
            - However, the remaining *Fatty Marrow*, *Liver & Spleen* can resume their "extramedullary haematopoietic" roles in *Times of Need.*

Haematopoietic Stem Cells:

- Haematopoiesis starts with ***PluriPotent Stem Cells*** in the bone marrow.
- Self-renewing
- Differentiate & Divide to give rise to the separate cell lineages.
    - Erythroid → RBCs
    - Granulocytic → Granulocytes (Neutrophils/Eosinophils/Basophils)
    - Monocytic → Macrophages
    - Megakaryocytic → Platelets
    - Lymphoid → Lymphocytes (T&B)
    - Etc…see diagram.
- Considerable amplification – ie. 1 Stem Cell can produce 10,000,000 blood cells after only 20 divisions.
- Leukemias can result from defective haematopoietic stem cell lines;
    - Some people may need bone marrow transplants to replace/regenerate the stem cell pool.

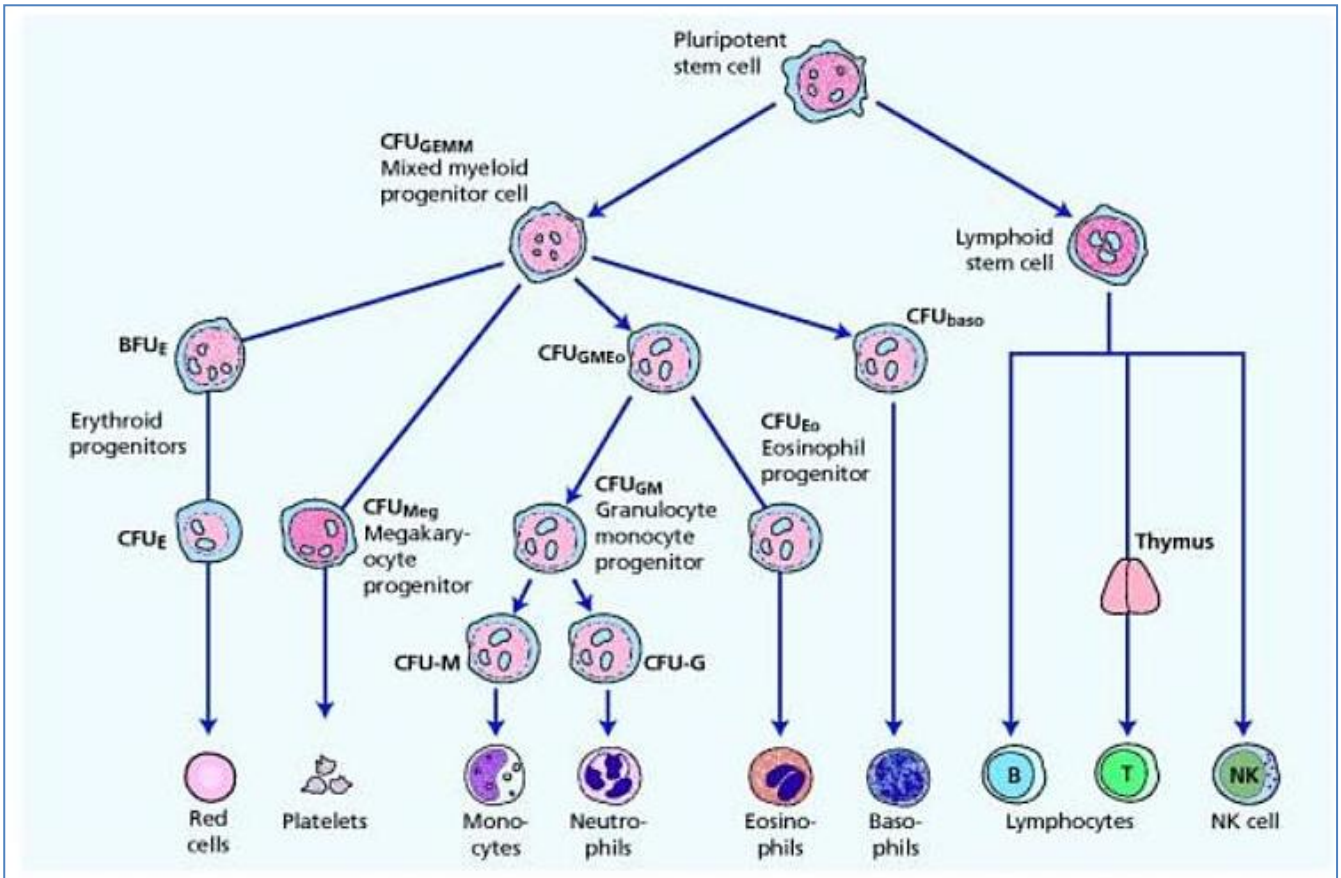
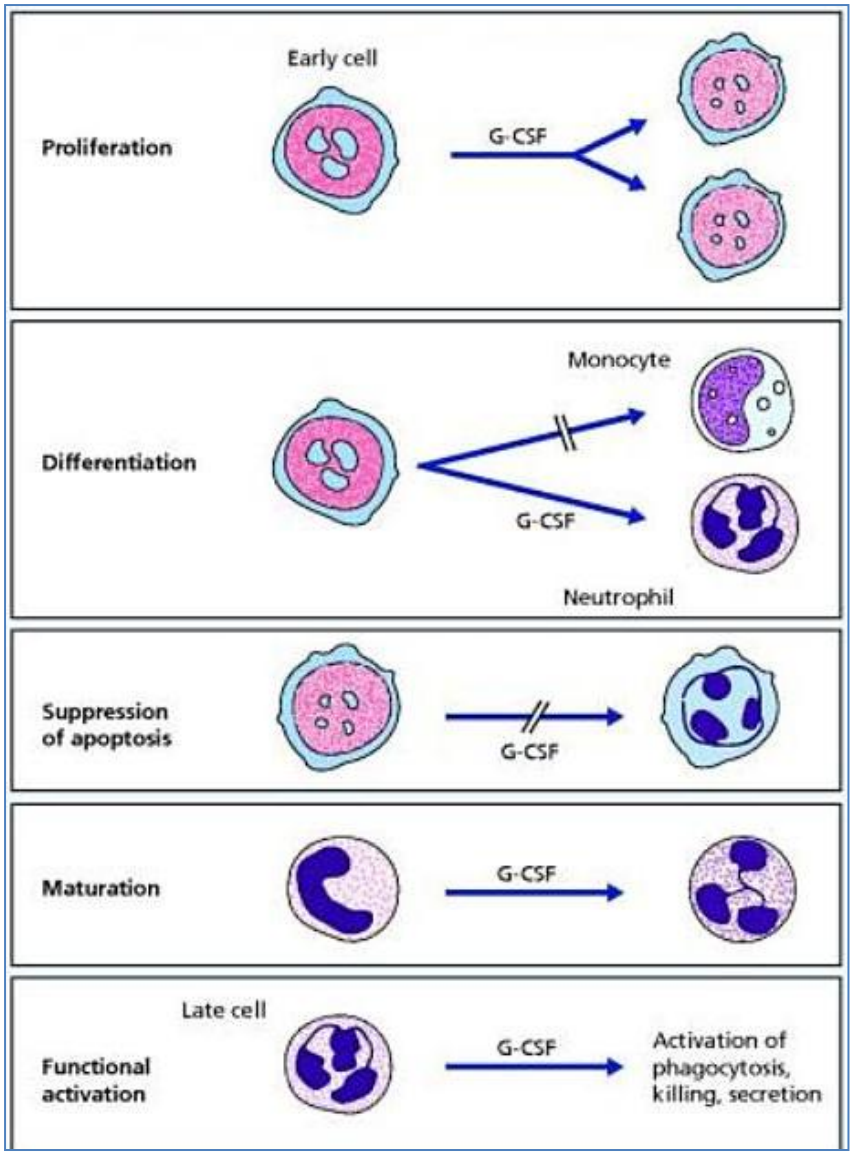


Fig. 1.2 Diagrammatic representation of the bone marrow pluripotent stem cell and the cell lines that arise from it. Various progenitor cells can be identified by culture in semi-solid medium by the type of colony they form. Baso, basophil; BFU, burst-forming unit; CFU, colony-forming unit; E, erythroid; Eo, eosinophil; GEMM, granulocyte, erythroid, monocyte and megakaryocyte; GM, granulocyte, monocyte; Meg, megakaryocyte; NK, natural killer.

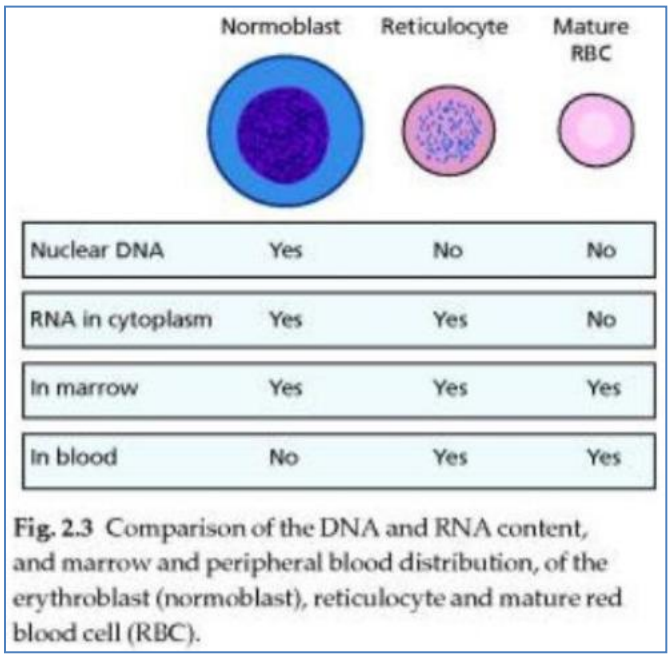
Haematopoietic Growth Factors

- Regulation of Haematopoiesis
  - Control *Growth* & *Differentiation*
  - Can Stimulate Cell Maturation
  - Can Suppress Apoptosis
  - Can Affect the Function of Mature, Non-Dividing Cells.



Erythropoiesis:

- Red Blood Cell Formation
- A sequence of *Amplification* & *Maturation*.
    - Stem Cells → CFU's → BFU's →The 1st recognisable erythrocyte precursor: The **Pronormoblast.**
        - Pronormoblast → progressively smaller Normoblasts → **Reticulocytes** (no nucleus – but DNA & RNA remnants)
- Responsible for 10^{12} new erythrocytes each day
- Finely Regulated



	Normoblast	Reticulocyte	Mature RBC
Nuclear DNA	Yes	No	No
RNA in cytoplasm	Yes	Yes	No
In marrow	Yes	Yes	Yes
In blood	No	Yes	Yes

Fig. 2.3 Comparison of the DNA and RNA content, and marrow and peripheral blood distribution, of the erythroblast (normoblast), reticulocyte and mature red blood cell (RBC).

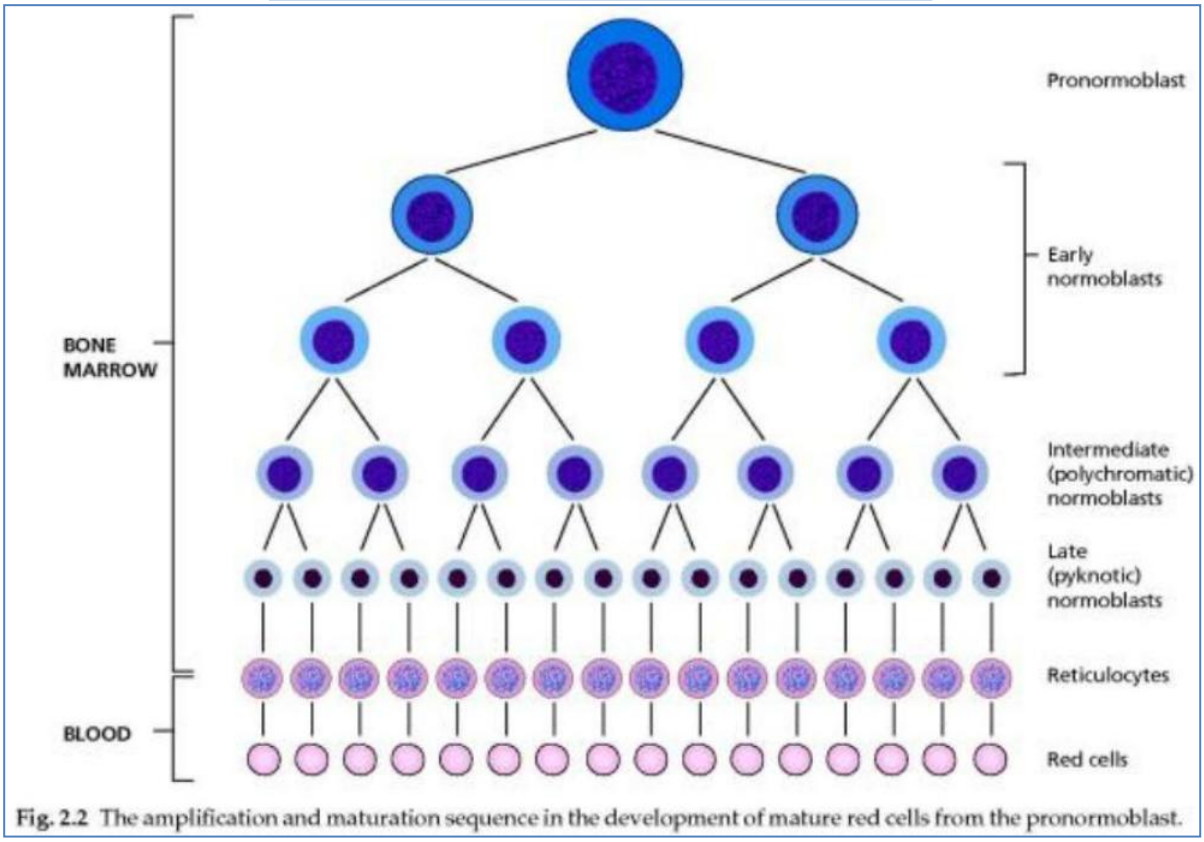
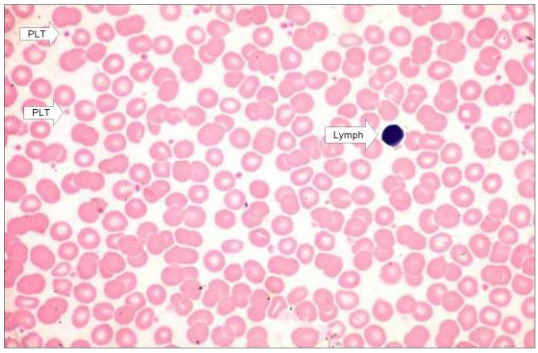


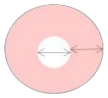
Fig. 2.2 The amplification and maturation sequence in the development of mature red cells from the pronormoblast.

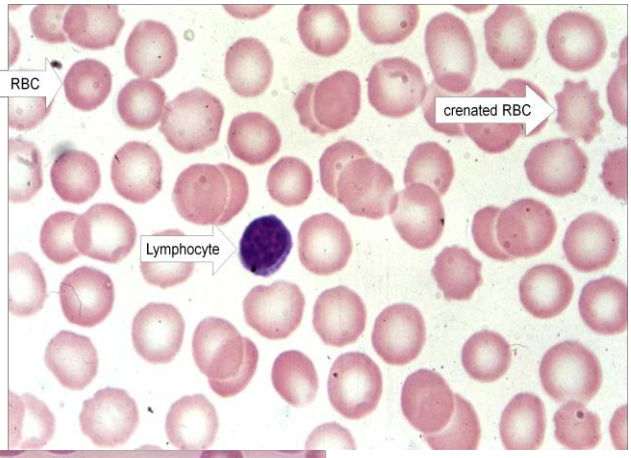
NB_1: As erythrocyte precursors mature, they ***gain haemoglobin*** & ***lose nuclear material.***

NB_2: Reticulocytes circulate in peripheral blood (1-2 days) before maturing in the *Spleen*.

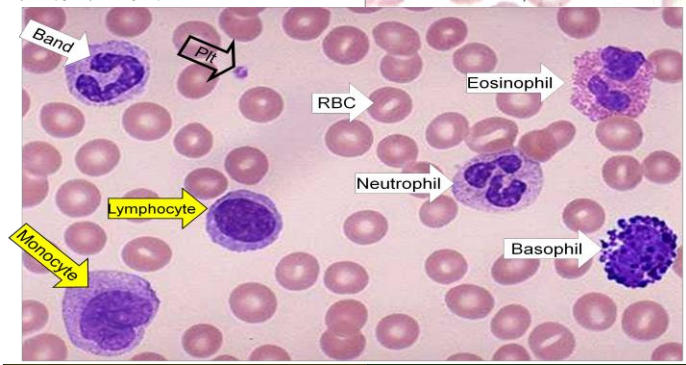
- **Normal Blood Smears:**
  - **RBCs:**
    - Most of the RBCs are round, have central pallor.
    - RBC's size is comparable to a small lymphocyte
  - **Other Cells:**
    - Neutrophils
    - Basophils
    - Eosinophils
    - Lymphocytes
    - Monocytes/Macrophages
      - (The difference is location – Monocytes in Blood, Macrophages in Tissues)
    - Platelets





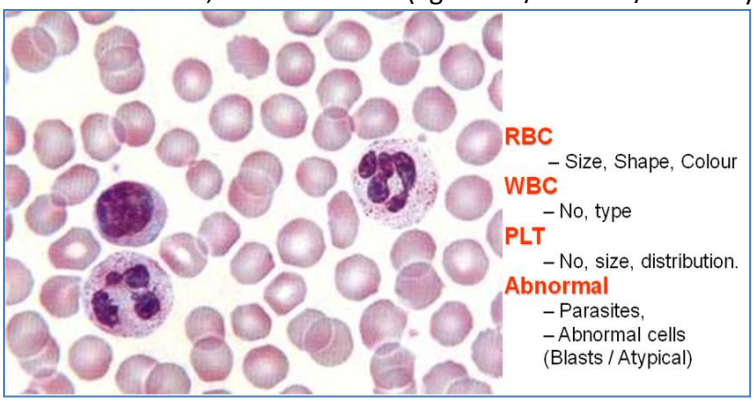


RBC Many - bright pink, central pallor.
PLT Some - small particles, purple.
WBC Few - Blue – purple (lymphocyte)



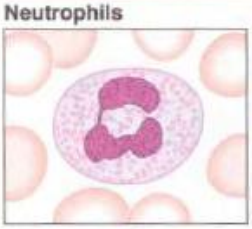
Non granular, Mononuclear Leukocytes | Granulocytic Polymorphs Leukocytes

- **System for Looking at Blood Smears:**
  - **1. RBC –** Assess Size, Colour, Shape.
  - **2. WBC –** Number, Types
  - **3. Platelets –** Number, Size, Distribution
  - **4. Abnormalities –** Parasites, Abnormal Cells (Eg. Sickle/Infected/Schistocytes/Blasts/Atypical/Etc.)



- **Causes of Abnormal White Cell Counts:**
  - **(NB: Philia = Too Many)**
  - **(NB: Penia = Too Few)**

Neutrophils



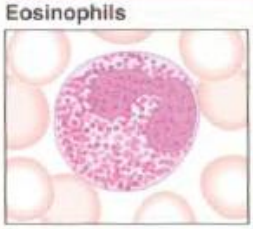
Causes of neutrophilia

- Infection
  - Bacterial
  - Fungal
- Trauma
  - Surgery
  - Burns
- Infarction
  - Myocardial infarct
  - Pulmonary embolus
  - Sickle-cell crisis
- Inflammation
  - Gout
  - Rheumatoid arthritis
  - Ulcerative colitis
  - Crohn's disease
- Malignancy
  - Solid tumours
  - Hodgkin's disease
- Myeloproliferative disease
  - Polycythaemia
  - Chronic myeloid leukaemia
- Physiological
  - Exercise
  - Pregnancy

Causes of neutropenia

- Infection
  - Viral
  - Bacterial; *Salmonella*
  - Protozoal; malaria
- Drugs
  - See Table 11.1
- Autoimmune
  - Connective tissue disease
- Alcohol
- Congenital
  - Kostmann's syndrome

Eosinophils



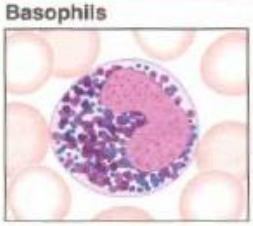
Causes of eosinophilia

- Allergy
  - Hay fever
  - Asthma
  - Eczema
- Infection
  - Helminths
  - Viral
- Skin disease
- Connective tissue disease
  - Polyarteritis nodosa
- Malignancy
  - Solid tumours
  - Lymphomas
- Drugs
  - Gold

Causes of eosinopenia

- Acute inflammation
- Drugs
  - Steroids
  - Catecholamines

Basophils



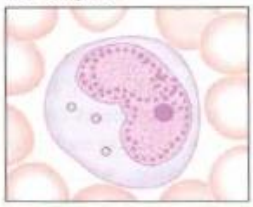
Causes of basophilia

- Myeloproliferative disease
  - Polycythaemia
  - Chronic myeloid leukaemia
- Inflammation
  - Acute hypersensitivity
  - Ulcerative colitis
  - Crohn's disease
- Iron deficiency

Causes of basopenia

- Hyperthyroidism

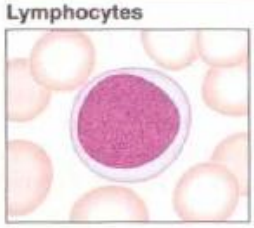
Monocytes



Causes of monocytosis

- Infection
  - Bacterial; TB
- Inflammation
  - Connective tissue disease
  - Ulcerative colitis
  - Crohn's disease
- Malignancy
  - Solid tumours

Lymphocytes



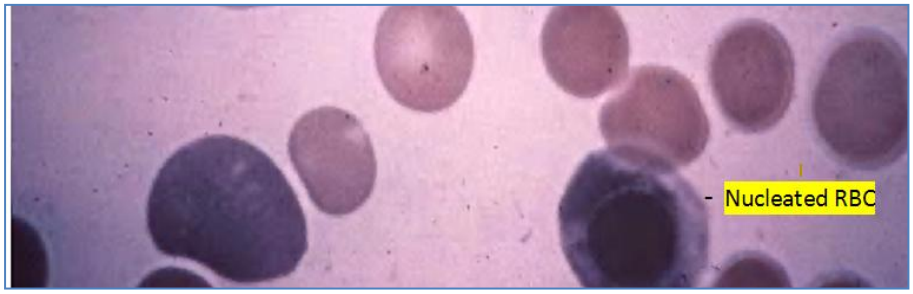
Causes of lymphocytosis

- Infection
  - Viral
  - Bacterial, *Bordatella pertussis*
- Lymphoproliferative disease
  - Chronic lymphatic leukaemia
  - Lymphoma
- Post-splenectomy

Causes of lymphopenia

- Inflammation
  - Connective tissue disease
- Lymphoma
- Renal failure
- Drugs
  - Steroids
  - Cytotoxics
- Congenital
  - Severe combined immunodeficiency

NB$_3$: Excess Reticulocytes in blood can be indicative of Anaemia (ie. The body's effort to compensate for lack of O_2)



NB$_4$: Severe Anaemia can result in nucleated RBC's in the blood (not good)

Regulation of Erythropoiesis:

- *Total Number of Erythrocytes* is finely regulated.
- **Erythropoietin:**
  - Erythropoiesis is regulated by the ***Hormone 'Erythropoietin'***
    - Produced by the *PeriTubular Interstitial Cells* of the *Kidneys*. (Also produced by liver <10%)
      - Erythropoietin Production – regulated by Oxygenation of Tissues in Kidneys.
      - Therefore Production INCREASES when:
        - Body is Anaemic
        - Haemoglobin isn't giving up O_2 normally (eg. CarbonMonoxide Poisoning)
        - Atmospheric [O_2] is low
        - Damage to Renal Circulation (ie. Ischemia of Kidney)
      - Production DECREASES when:
        - Tissue Oxygenation is Normal.

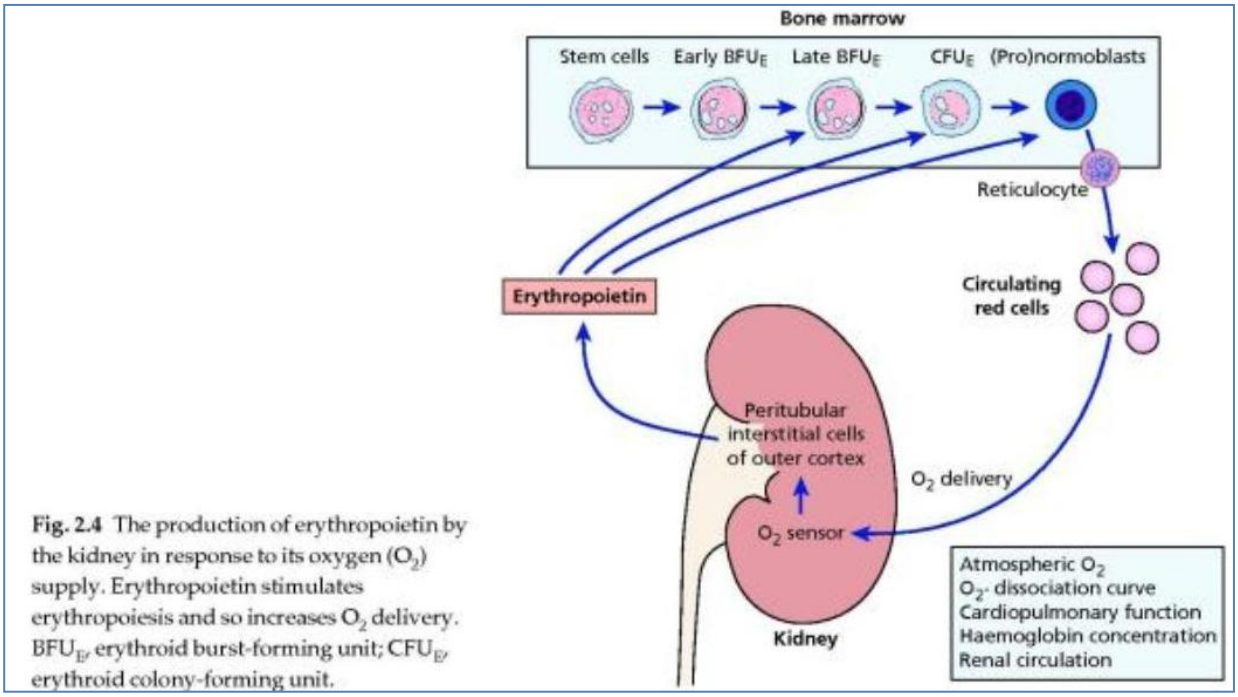
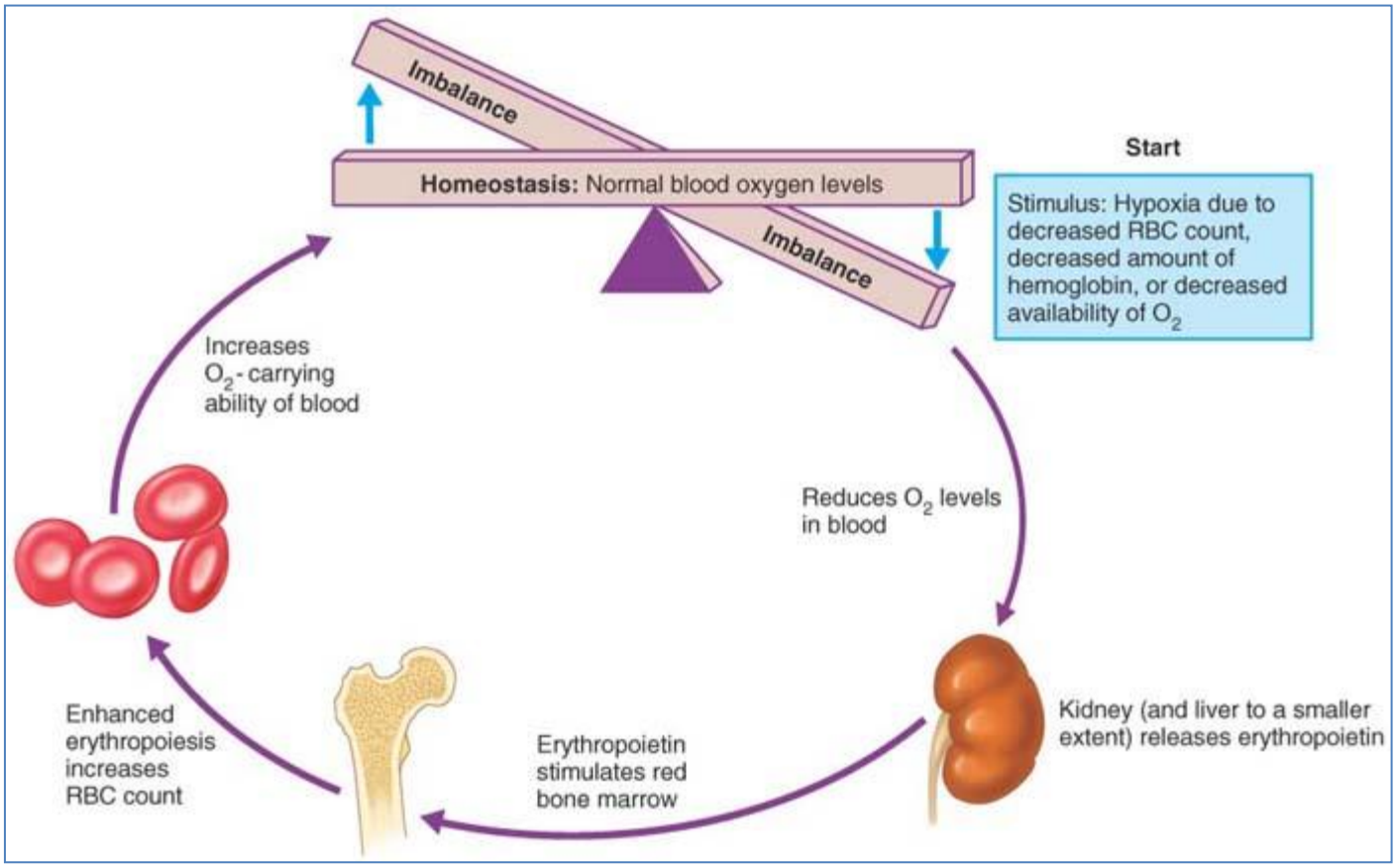


Fig. 2.4 The production of erythropoietin by the kidney in response to its oxygen (O_2) supply. Erythropoietin stimulates erythropoiesis and so increases O_2 delivery. BFU$_E$, erythroid burst-forming unit; CFU$_E$, erythroid colony-forming unit.



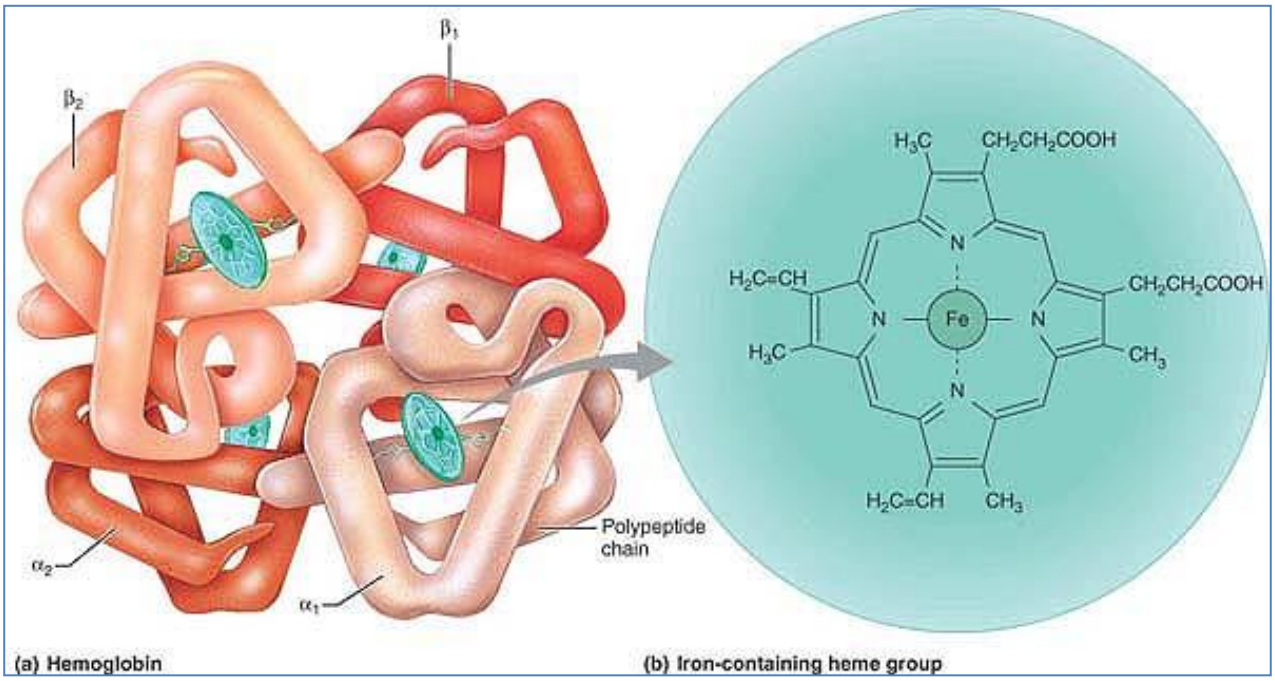
- **Mechanism:**
  - Stimulates Erythropoiesis by Increasing Progenitor Cells Committed to Erythropoiesis:
    - Via *Transcription Factors* → Enhance *Expression* of Erythroid-Specific Genes. (eg. Haemoglobin)

Requirements for Erythropoiesis & Haemoglobin Formation:

- The *Marrow* requires other precursors for effective erythropoiesis: eg.
  - **Metals:**
    - Iron – essential for Haemoglobin synthesis
    - Cobalt
  - **Vitamins:**
    - Especially Vit. B_{12} - necessary for normal DNA synthesis
    - Folate - necessary for normal DNA synthesis
    - Vit. C
    - Vit. E
    - Vit. B_6
    - Thiamine
    - Riboflavin
    - Pantothenic Acid
  - **Amino Acids:**
    - For the production of proteins
  - **Hormones:**
    - ***Erythropoietin***
    - Androgens
    - Thyroxine
    - Interleukin-3
    - GM-CSF (Granulocyte & Macrophage – Colony Stimulating Factor)

Haemoglobin:

- **Functions:**
  - To carry O_2 to tissues
  - To Return CO_2 from tissues → Lung
  - Storage pool of Iron. (65% of bodily Iron is in Haemoglobin)
- **Constituents:**
  - Made up of the protein ***globin*** bound to the red ***heme*** pigment.
  - Most common Adult Haemoglobin Molecule = Hb'A'
  - *Globin* consists of *4 Polypeptide Globulin* chains – each with its own *Haem Group*.
    - 2 Alpha
    - 2 Beta
  - Haem Molecules (Groups)....containing:
    - Protoporphyrin:
      - Combines with iron in the Ferrous (Fe^{2+}) State to form Haem.
    - 1x Iron atom in its centre:
      - Each Iron atom can combine with 1x molecule of Oxygen....therefore:
        - 1x Haemoglobin molecule can transport 4x molecules of Oxygen
- **Oxygen Loading:**
  - In lungs
  - O_2 diffuses into blood → into erythrocytes → binds to Iron Molecules in Haemoglobin.
  - Haemoglobin → Becomes **OxyHaemoglobin**:
    - Assumes a new 3D shape
    - Becomes Ruby Red
- **Oxygen UnLoading:**
  - In Tissues
  - O_2 detaches from Iron Molecules in Haemoglobin → Out of RBC, into blood → O_2 into Tissue
  - OxyHaemoglobin → Becomes **DeOxyHaemoglobin:**
    - Resumes its former 2D shape
    - Becomes **Dark** Red.
- **CO_2 Transport:**
  - CO_2 binds to Globin's Amino Acids ...Rather than on the Haem Group.



Haemoglobin – Oxygen Dissociation Curve:

- Oxygen exchange operates between 95% Saturation (Arterial Blood) & 70% Saturation (Venous Blood)
- P_{50} = Partial Pressure of O_2 at which Haemoglobin is ½ saturated with O_2. (26 mmHg)
- As the curve *shifts to the right*, O_2 is given up *More Readily* to the Tissues.
- During *CO_2 Unloading* in the lungs, the curve *shifts to the left,* → O_2 uptake increases.

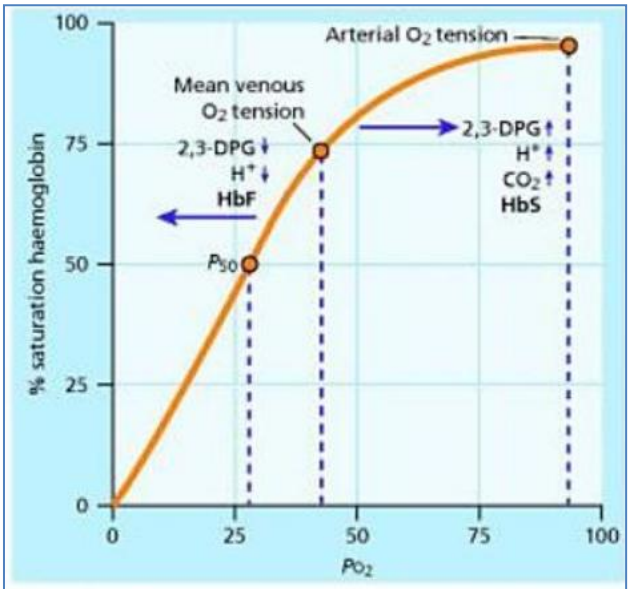
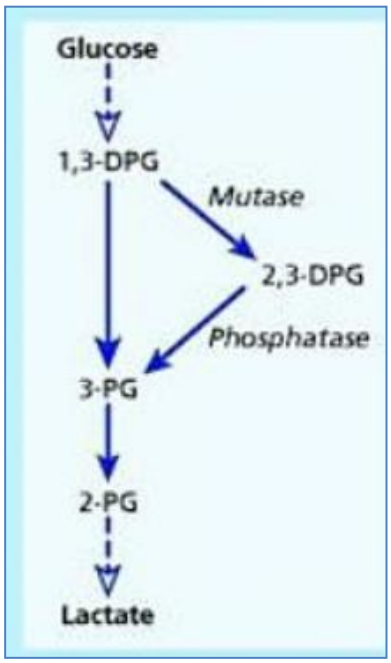


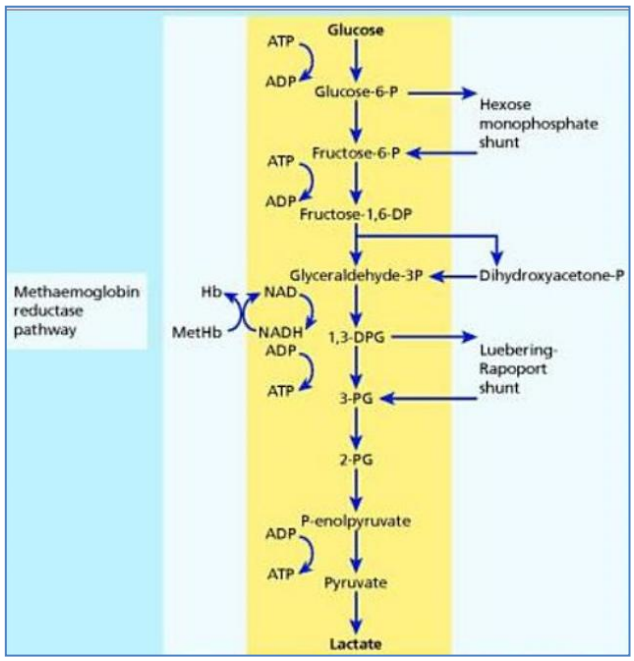
Fig. 2.9 The haemoglobin oxygen (O_2) dissociation curve. 2,3-DPG, 2,3-diphosphoglycerate.

Erythrocyte Metabolism:

- Because RBC's don't have Mitochondria, they're forced to generate energy via ***anaerobic pathways***:
- **Embden-Meyerhof Pathway:**
  - Glucose metabolised to ATP
- **Pentose-Phosphate Pathway** (aka. Hexose Monophosphate Shunt)**:**
  - Glucose metabolised to NADPH
  - NADPH – used by *Methaemoglobin Reductase* to maintain Haemoglobin-Iron in *Ferrous Form* (Fe^{2+})
    - Iron in the *Ferric Form* is useless because it doesn't bind oxygen. → Leads to Oxidative Stress



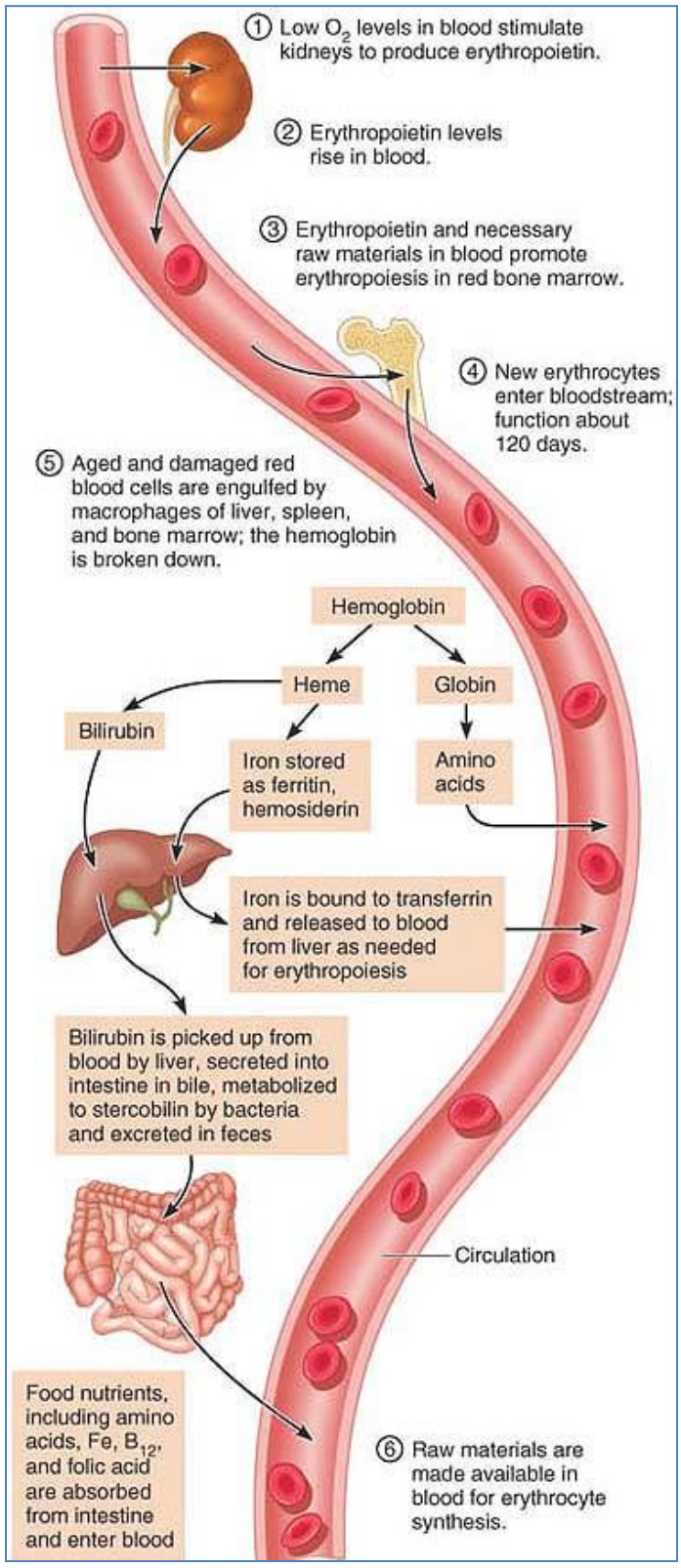
Embden-Meyerhof Pathway



Shows the Pentose Phosphate Pathway
(Aka. Hexose Monophosphate Shunt).

Erythrocyte Death:

- Average Erythrocyte Lifespan: 120 Days
- Beyond 100 Days:
  - Glycolysis slows
  - ATP levels decline
  - Membrane becomes less flexible
- Dying Cells – Removed by Macrophages in Spleen & Liver
  - Iron is reused → Transported back to Bone Marrow (bound to *Transferrin*) → Stored as *Ferritin* in Bone Marrow.
  - Protoporphyrin (Haeme minus Iron) is metabolized → Bilirubin → Conjugated in Liver → Excreted in Bile.



Classifying Anaemia

Introduction to Anaemia:

- **Definition:** ***A Lower-Than-Normal Haemoglobin Concentration.*** (generally less than 100g/L)
- Normal Hb Concentration depends on age/sex/geographical location.
- **More Common In:**
    - Pregnant Women
    - Children under 5yrs
    - Low SES people – due to poor diet/nutrition.

Measuring Anaemia:

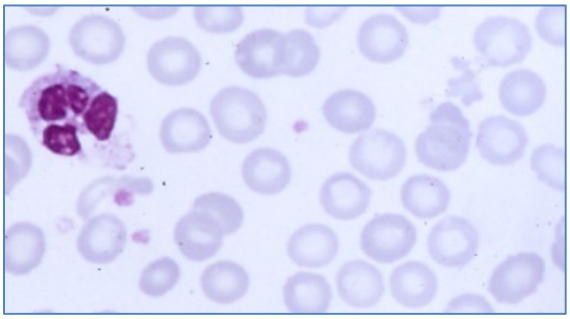
- **Via Red Cell Indexes:**
    - **Mean Cell Volume (MCV):**
        - Average size of RBC
        - Described as:
            - Microcytic (smaller than normal)
            - Normal
            - Macrocytic (larger than normal)
    - **Mean Cell Haemoglobin (MCH):**
        - The average *amount of haemoglobin in the average RBC*.
        - Derived from the measurement of haemoglobin and the red cell count.
            - The haemoglobin value = amount of haemoglobin in a volume of blood
            - The red cell count = number of red blood cells in a volume of blood.)
        - The normal range for the MCH is 27 - 32 picograms.
    - **Mean Cell Haemoglobin Concentration (MCHC):**
        - The average *concentration of haemoglobin in a given volume of blood*.
        - Derived from the measurement of haemoglobin and the haematocrit.
            - Haemoglobin value = amount of haemoglobin in a volume of blood while the hematocrit is the ratio of the volume of red cells to the volume of whole blood.) The normal range for the MCHC is 32 - 36%.
- **Staining:**
    - Normal RBCs stain well – **(Normochromic)**
    - Anaemic cells stain lightly - **(Hypochromic)**
- **Morphological Classification (Size):**
    - **Microcytic:** Small - Reduced MCV
    - **Normocytic:** Normal MCV
    - **Macrocytic:** Large – Increased MCV

Causes of Anaemia:

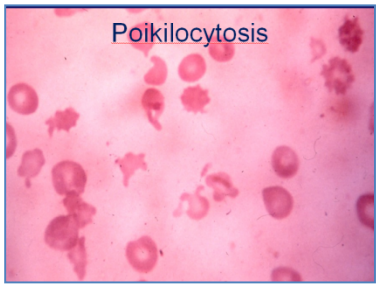
- Severe RBC loss (Eg. Bleeding)
- Increased Haemolysis (Eg. Parasitic Infections – malaria)
- Failure of Production (Eg. Nutritional Deficiency/RBC Malformation/↓Bone Marrow Cells)
- Abnormal RBC Shape/Function
- Dilution of RBCs due to Increased Plasma Volume (Eg. Pregnancy – body retains more fluid – kidneys don't eject as much – plasma volume increases)

3 Common Anaemic Combinations:

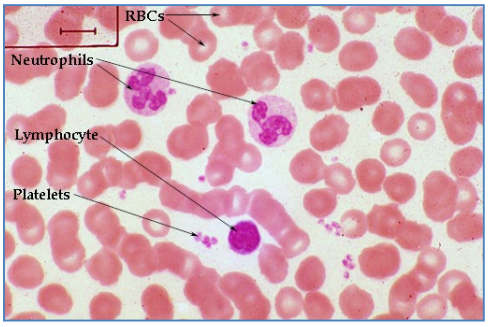
- **1. Microcytic & Hypochromic:** (Small & Non-Staining)



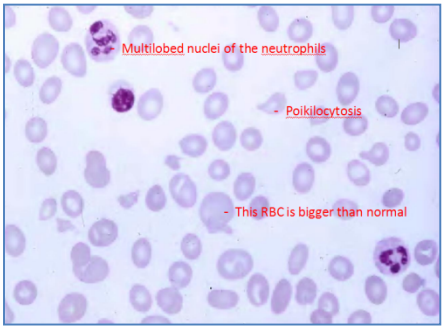
  - **Iron Deficiency (Typically):**
    - Low Iron Stores
    - Due to:
      - Chronic blood loss
      - Increased demands
      - Menstruation
      - ↓Diet Iron Intake (Rarely *sole* cause)
    - Commonest cause of Anaemia
    - Iron is needed for Haemoglobin production (& RBC production)
    - ↓Iron Stores → ↓Erythropoiesis
  - **Chronic Inflammation:**
    - Lack of Fe Release from Macrophages in Bone Marrow → Plasma
    - ↓RBC lifespan
    - ↓Erythropoietin Response → ↓Erythropoiesis
  - **Sideroblastic Anaemia:**
    - Failure of Protoporphyrin synthesis (precursor of Heme)
  - **Thalassaemias:**
    - ↓ Synthesis of Alpha/Beta Globin chains – Haemoglobin Disorder - Ineffective erythropoiesis
    - ↑ Haemolysis – due to aggregation of unmatched globin chains
    - May exhibit *Poikilocytosis* (RBCs – weird shapes/sizes)
    - **Alpha Thalassaemia:**
      - Deletion of 1/more of the 4 Alpha Globin genes.
    - **Beta Thalassaemia:**
      - Mutations in the Beta Globin genes – prevent B-chain formation.



- **2. Normocytic & Normochromic:** (Normal Size & Colour)
  - Typically from Acute Blood Loss
  - Technically anaemic, but only due to ↓ Blood Volume



- **3. Macrocytic & Normochromic:** (Large & Normal Colour)

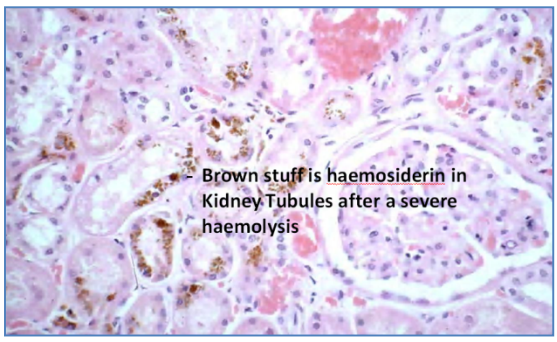


  - Typically from defective nuclear maturation of erythroblasts.
    - Due to defective DNA synthesis
      - Due to ↓$VitB_{12}$/Folate
  - Another cause: Alcoholism
  - Some Haemolysis – due to bigger RBCs (can't fit through capillaries)
  - Neutrophils – hypersegmented nuclei

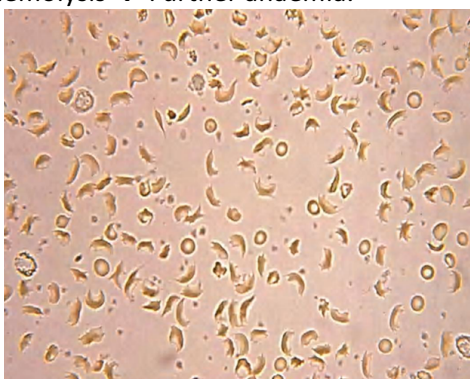
  - **Causes of $VitB_{12}$ Deficiency:**
    - **Nutritional** – Lack of V_{B12} Dietary Intake.
    - **Gastric** – Abnormality of *Intrinsic Factor* (Eg. Perncious Anaemia – autoimmune response to parietal cells of stomach → ↓IF → ↓$VitB_{12}$ Absorption)
    - **Intestinal –** eg. Resected Ileum/Crohn's Disease
  - **Causes of Folate Deficiency:**
    - **Nutritional** – Lack of Folate Dietary Intake
    - **Malabsorption –** eg. Coeliac Disease/Intestinal Resection.
    - **Excess Utilization –** eg. Pregnancy/Lactation/Chronic Inflammation/Cancers
    - **Excess Urinary Loss –** eg. Acute Liver Disease/Congestive Heart Disease.

Other Anaemias:

- **Haemolytic Anaemia:**
  - Abnormal *Destruction* of RBCs
  - Where RBC lifespan ↓↓ & Bone-Marrow RBC Production can't keep up.
  - **Causes:**
    - Other Anaemias – eg. Macrocytic/Thalassaemias
    - **Inherited:**
      - Cell Membrane Defect – eg. Elyptocytosis
      - Naemoglobin – Thalassaemias/Sickling Disorders
      - Metabolic Disorders – G6P-Dehydrogenase Deficiency / Pyr.Kinase Deficiency
    - **Acquired:**
      - Immune – Autoimmune Haemolytic Anaemia
      - Isoimmune – Blood-Type Incompatibility (eg. Transfusion Reaction)
      - Non-Immune – Infection/Drug Side Effects/Hypersplenism (Hyperactive Spleen)
  - **Results:**
    - Elevated Free-Hb in Blood (*Haemoglobinaemia*)
    - Hb in Urine (*Haemoglobinuria*) → Red-Brown Urine.
    - Haemosiderin (iron from Hb) in Urine (*Haemosiderinurial*)



- **Sickle Cell Anaemia:**
    - Inherited
    - Prevalent in Afro-Carribean populations.
    - Abnormal Beta-Haemoglobin Chain
        - Abnormal Hb – Insoluble – Forms crystals @ low O_2 Tension
        - Leads to sickle-shaped RBC → Clogs small capillaries → Tissue Necrosis.
        - Episodes of haemolysis → Further anaemia.



SS Questions – Possible KFP Qs

Question 1

The children of a family of low socio-economic status have been diagnosed with iron deficiency anaemia. What might be the cause(s) of the anaemia and what are the key clinical and laboratory findings. How would you explain to the family the key elements of the normal iron cycle in the body?

- Causes: Poor nutrition due to low SES.
- Clinical & Laboratory Findings: Hypochromic and Microcytic Red blood cells.
- Normal Iron Cycle: Iron stored in body in 3 forms: Haem in Haemoglobin , Haemosiderin & Ferritin in muscle
    - Erythrocytes die and break down
        - Haemoglobin broken into Haem & Globin.
            - Haem --> turned into bilirubin & iron
                - Iron --> stored in liver as Haemosiderin & ferritin
                    - Iron bound to transferrin --> Released into blood from liver --> Erythropoiesis
    - Iron is lost in urine, skin, menstruation, sweat etc. See P29 of essential haem.

Question 2

A 60 year old grandmother of Northern European ancestry has been diagnosed as having pernicious anaemia. Explain the pathogenesis of this form of anaemia.

- Caused by atrophy o the parietal cells of the stomach --> no intrinsic factor production --> No Bit B12 absorption --> Macrocytic Anaemia

Question 3

A 30 year old Australian was on a camping holiday in Europe developed an illness characterized by a fever and jaundice. He and travelling companions had been camping in fields where cattle were grazing. He had had his spleen removed following a car accident on his 20th birthday. Examination of a blood smear showed the presence of the protozoan parasite *Babesia divergens* within many of his red blood cells. Explain how jaundice developed in this case.

- Parasite in blood cells causes blood cells to break down
- Spleen isn't there to break down abnormal blood cells
- Protoporphyrin from lysed red blood cells --> metabolised to bilirubin --> too much bilirubin in blood --> can;t all be conjugated to be excreted in the bile --> jaundice.

Haemostasis

What is Haemostasis?

- Literally means "Blood Halting"....i.e. Stopping Bleeding
- When a blood vessel breaks, Haemostasis is responsible for 'plugging' the hole.
  - Without Haemostasis, we would 'bleed-out' from even the smallest cuts.
- The Haemostatic Response is ***Fast***, ***Localised & Finely Regulated.***
  - Involves a chain reaction of 12 *Blood Coagulation FACTORS (Procoagulants)*:...see table below
    - (Normally Present In Plasma)
  - Also involves some other substances released by platelets and injured tissue cells.
- Results in a stable '*Platelet Plug'* (clot) at the site of injury.

TABLE 17.3 Blood Clotting Factors (Procoagulants)

FACTOR NUMBER	FACTOR NAME	NATURE/ORIGIN	FUNCTION OR PATHWAY
I	Fibrinogen	Plasma protein; synthesized by liver	Common pathway; converted to fibrin, insoluble weblike substance of clot
II	Prothrombin	Plasma protein; synthesized by liver; formation requires vitamin K	Common pathway; converted to thrombin, which enzymatically converts fibrinogen to fibrin
III	Tissue factor (TF) or tissue thromboplastin	Glycoprotein in plasma membrane of cells underneath the endothelium	Activates extrinsic pathway
IV	Calcium ions (Ca^{2+})	Inorganic ion present in plasma; acquired from diet or released from bone	Needed for essentially all stages of coagulation process
V			Common pathway
VI	Number no longer used; substance now believed to be same as factor V		
VII			Both extrinsic and intrinsic mechanisms
VIII			Intrinsic mechanism
IX			Intrinsic mechanism
X			Common pathway
XI			Intrinsic mechanism
XII			Intrinsic mechanism; activates plasmin; initiates clotting in vitro; activation initiates inflammation
XIII	Fibrin stabilizing factor (FSF)	Plasma protein; synthesized in liver and bone marrow	Cross-links fibrin, forming a strong, stable clot

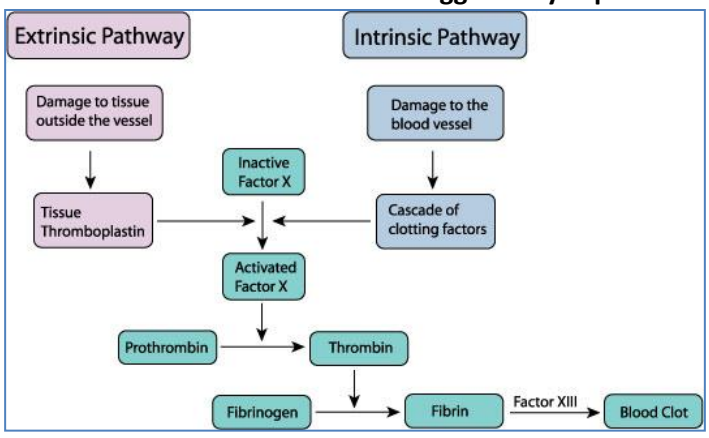
SIMPLIFIED SUMMARY of Haemostasis.

- **3 Phases of Haemostasis:**
  - **1. Primary Haemostasis:**
    - **Vascular Spasms:**
      - Vasoconstriction: The immediate response to vessel damage.
    - **Primary Platelet Plug Formation:**
      - When vessel is damaged → ***Sub-Endothelial Collagen*** is exposed....
        - Platelets ***(+ Von Willebrand Factor*** [glue]***)*** adhere strongly to the Collagen Fibres...
        - Primary Platelet-Plug 'Sandwich':

          Surface Glycoproteins on Platelets

          Von Willebrand Factor

          Sub-Endothelial Collagen
    - **Platelet Aggregation:**
      - Once attached, Platelets → Activated → ***Release Several Chemicals:***
        - **Serotonin:** Vasoconstrictor
        - **ADP:** Potent Platelet-Aggregating Agent
        - **Calcium (Factor IV):** A cofactor that *Activates* other *Inactive Pro-Coagulation Factors*. :. Important in Coagulation
        - **Thromboxane A_2:** Vasoconstrictor Potent Platelet-Aggregating Agent
      - Initiates a Positive Feedback Cycle → Activates & Attracts more & more Platelets.
        - Within 1min, a platelet plug is built → further reduces blood loss.
  - **2. Secondary Haemostasis:**
    - **Coagulation Cascade:**
      - **Intrinsic Pathway:**
        - **→Triggered by Exposed Sub-Endothelial Collagen**
        - All factors needed for clotting are in the blood
      - **Extrinsic Pathway:**
        - **→Triggered by Exposed Tissue Factor** (Factor III)



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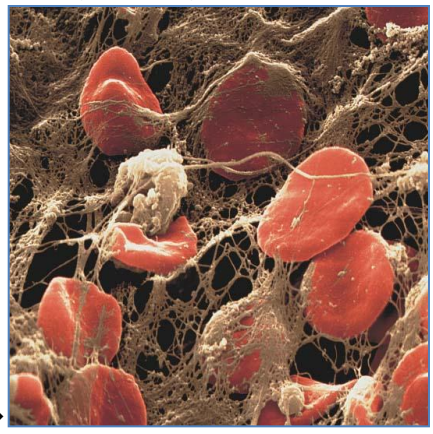
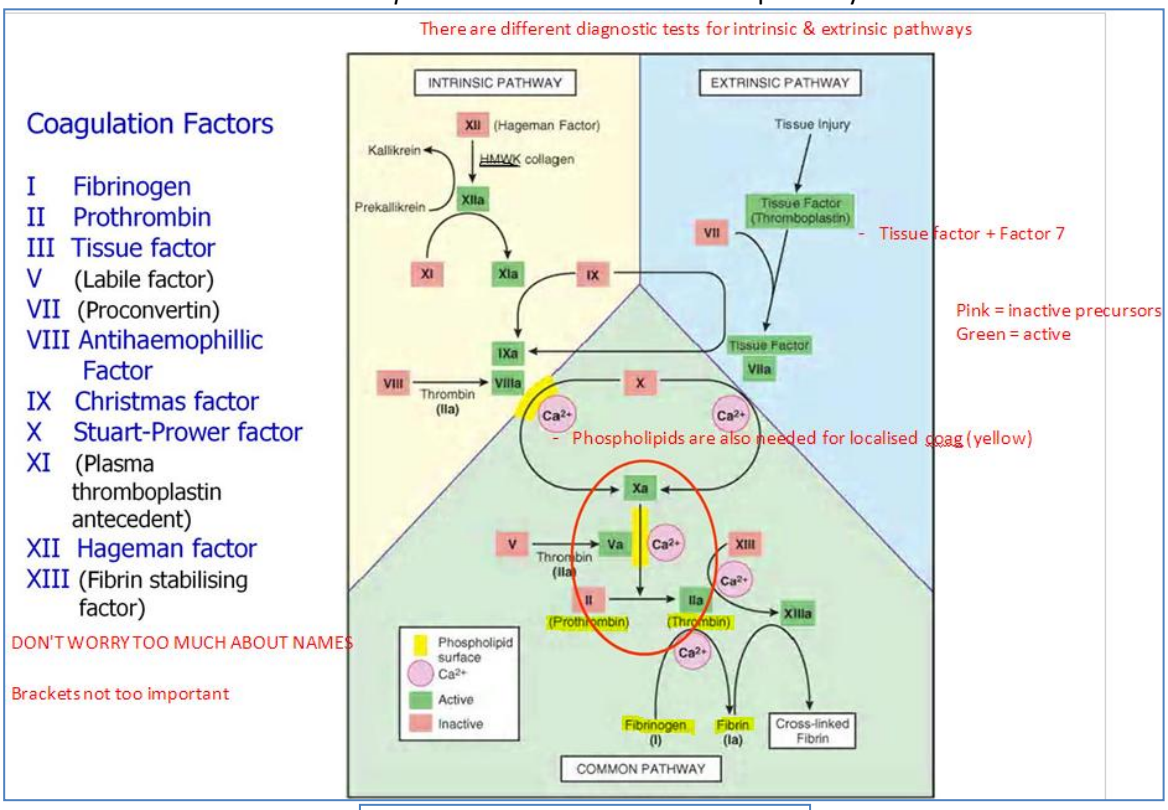
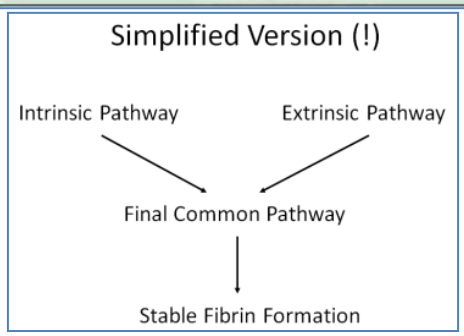


      - Both Pathways eventually lead to ***Activation of Factor-X***
  - **3. Fibrinolysis:**
    - Via a *Fibrin-Digesting Enzyme:* ***Plasmin*** → Degrades fibrin & :. The clot as well.
      - Plasmin: Produced when ***Plasminogen*** is activated.
      - **Plasminogen Activation:** (once clot is formed)
        - **Endothelial Cells:** secrete ***Tissue Plasminogen Activator (tPA)***
        - **Activated Factor XII:** also *Activates Plasminogen*
        - **Thrombin:** also *Activates Plasminogen*

SIMPLIFIED SUMMARY 2:

- **Coagulation Cascade – *THE FOCUS OF THIS WEEK*:**
  - **Intrinsic Pathway:**
    - Begins in the blood itself i.e. *intrinsic* to the blood
    - Initiated by activation of *Hageman Factor (Factor XII)*
  - **Extrinsic Pathway:**
    - Activated by damage to a vessel wall i.e. *extrinsic* to the blood
    - Initiated by *Tissue Factor (Factor III)*
  - **Common Pathway:**
    - Both Pathways → Formation of a: ***'Prothrombin Activator Complex' (PAC)***
    - PAC then activates final common pathway leading to formation of fibrin
  - **Formation and stabilization of Fibrin:**
    - Prothrombin → Thrombin
      - Fibrinogen → Fibrin
        - → Fibrin Deposition
- **NB: Calcium Ions:**
  - Essential for the coagulation cascade to function
  - Promote ***all*** reactions *except* the first two of the *intrinsic* pathway





The coagulation system is '***irreducibly complex***'

What does that mean? – Requires everything there for it to function. (An all or nothing process)

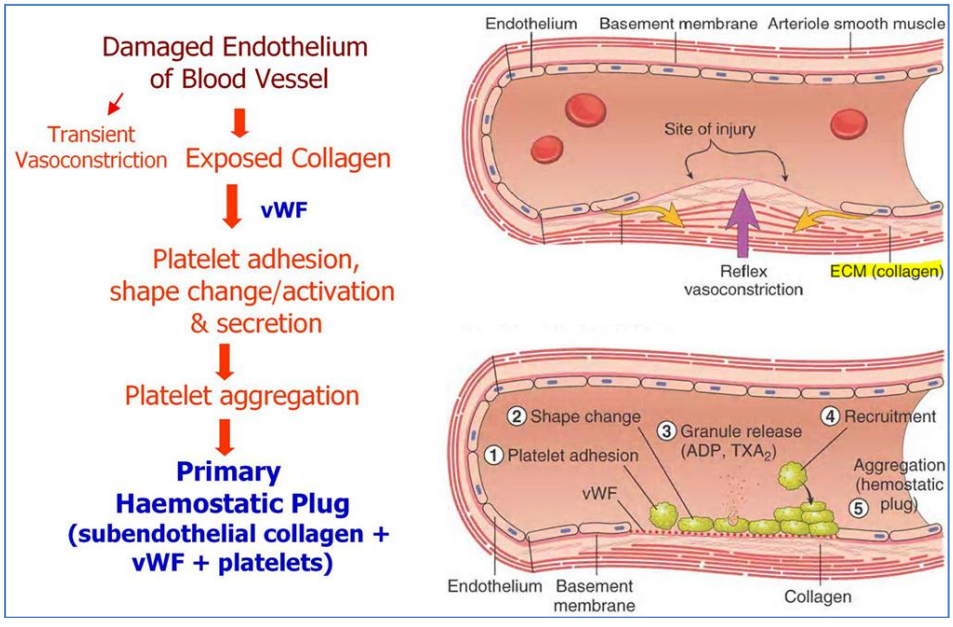
3 Phases of Haemostasis:

- **1. Primary Haemostasis:**
  - **Vascular Spasms:**
    - Vasoconstriction: The immediate response to vessel damage.
    - Triggered by:
      - Local Neural Pain-Reflexes
      - Chemicals released by: Endothelial Cells & Platelets
      - Direct Smooth Muscle Injury
    - Significantly reduces blood loss→ allows time for Platelet-Plug Formation & Clotting.
    - Most effective in smaller vessels.
  - **Primary Platelet Plug Formation:**
    - Platelets form a 'plug' → *Temporarily* seals the break in vessel wall
    - Platelets normally flow smoothly through an undamaged vessel.....HOWEVER....
    - When vessel is damaged → ***Sub-Endothelial Collagen*** is exposed....
      - Platelets ***(+ Von Willebrand Factor*** [glue]***)*** adhere strongly to the Collagen Fibres...
        - Platelets Activate → Conformational Change →
          - Swell
          - Form Spiked Processes
          - Become 'Sticky'.
      - Primary Platelet-Plug 'Sandwich':

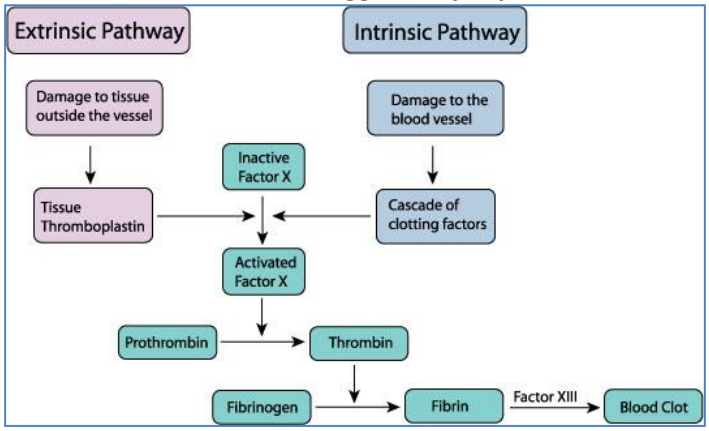
        Surface Glycoproteins on Platelets

        Von Willebrand Factor

        Sub-Endothelial Collagen
  - **Platelet Aggregation:**
    - Once attached, Platelets → Activated → ***Release Several Chemicals:***
      (Platelet Activation & Secretion Enhanced by Thrombin)
      - **Serotonin:** Vasoconstrictor
      - **ADP:** Potent Platelet-Aggregating Agent
      - **Calcium (Factor IV):** A cofactor that *Activates* other *Inactive Pro-Coagulation Factors*.
        :. Important in Coagulation
      - **Thromboxane A_2:** Vasoconstrictor
        Potent Platelet-Aggregating Agent
    - Initiates a Positive Feedback Cycle → Activates & Attracts more & more Platelets.
      - Within 1min, a platelet plug is built → further reduces blood loss.
  - **Platelet-Plug Localisation:**
    - **Prostacyclin:**
      - A Prostaglandin Produced by *Intact* Endothelial Cells.
      - A Strong *Inhibitor* of Platelet Aggregation



- **2. Secondary Haemostasis:**
  - **Coagulation Cascade:**
    - Coagulation (i.e. Blood 'Clotting'): Where Blood; Liquid → Gel
    - Series of enzymatic conversions of *Inactive Coag. Factors* → *Active Coag. Factors.*
    - **Intrinsic Pathway:**
      - →**Triggered by Exposed Sub-Endothelial Collagen**
      - All factors needed for clotting are in the blood
    - **Extrinsic Pathway:**
      - →**Triggered by Exposed Tissue Factor** (Factor III)



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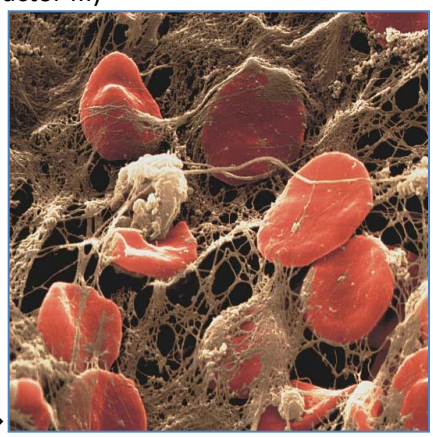
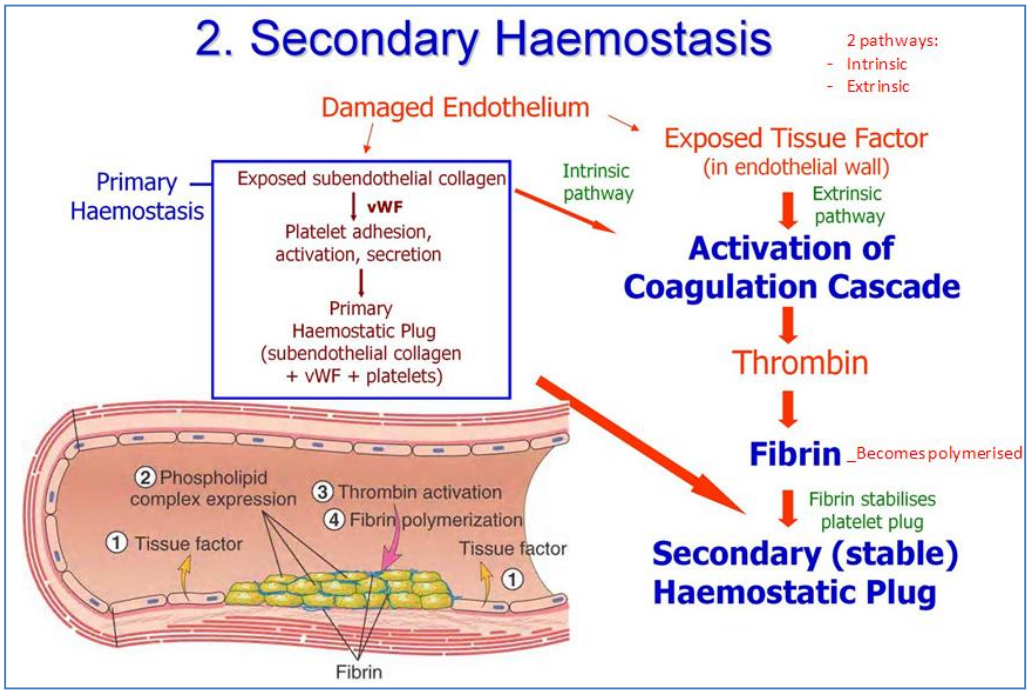
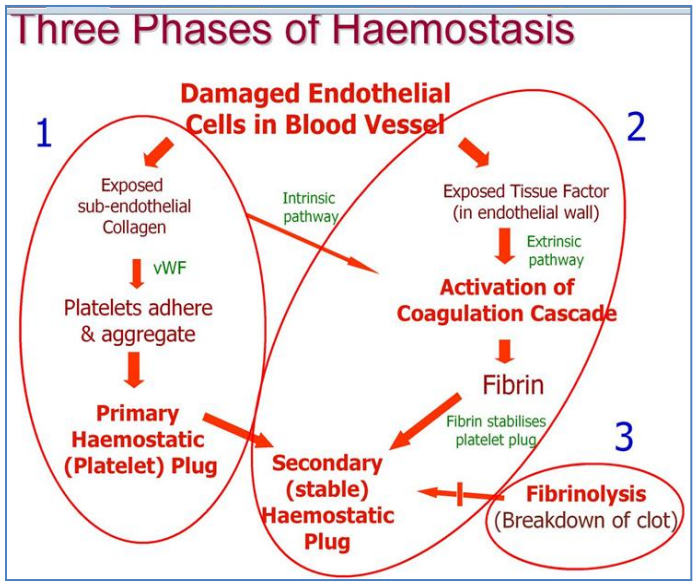


    - Both Pathways eventually lead to ***Activation of Factor-X***
      - **1. Activated Factor-X** combines with other factors→
      - **2. Prothrombin Activator** is formed...
      - **3. Prothrombin Activator**; converts the plasma-protein: ***Prothrombin → Thrombin*.**
  - **Fibrin Deposition:**
    - **4. Thrombin** Catalyses Conversion & Deposition of ***Fibrinogen →Fibrin***
      - Also **+Ve Feedback** on Coag. Cascade (Amplification of ProThrombin Activation)
    - **5. Fibrin** Mesh →+ ***Active Factor-XIII*** → Stabilises the Platelet-Plug → Seals the hole
      - **Primary Platelet Plug** + *Mesh* → **Secondary Platelet Plug.**
  - **Regulation:**
    - **ProCoagulants (Clotting Factors):**
      - Factors enhancing clot-formation (Factors I – XIII)
      - Most are plasma proteins (inactive) made by the liver
      - These factors Dominate in Damaged-Vessels
    - **AntiCoagulants:**
      - Factors inhibiting clot-formation
      - These factors Dominate in Undamaged-Vessels.
  - **Coagulation Localisation:**
    - **Activation of Coagulation Factors is Restricted to Sites of Exposed PhosphoLipids:**
      - I.e. PL's on platelet membranes
      - Platelet PL's are exposed by Platelet-Activation
    - **Anticoagulants:** See Above
      - **Tissue Factor Pathway Inhibitor:**
        - Inhibits Extrinsic Pathway..by:
        - Inactivates Factor-X_a
        - Inhibits [Factor-VII_a – Tissue Factor Complex]
      - **Thrombomodulin:**
        - Blocks Coag. Cascade
        - Binds Thrombin – Fibrinogen can't convert to Fibrin
          - Then Activates Protein-C
      - **Protein C & Protein S:**
        - Combine to *Inactivate Factor-V_a & Factor-$VIII_a$*.
      - **Antithrombin *(+ Heparin)*:**
        - Inhibits Thrombin
        - Inhibits Factor-X_a & Factor-XI_a



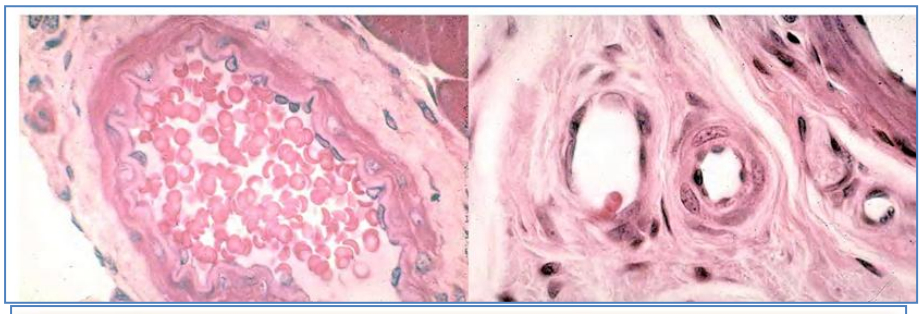
- **3. Fibrinolysis:**
  - Clots aren't permanent solutions to vessel injuries.
  - :. Fibrinolysis removes un-needed clots after healing has occurred...by:
  - **Blocking Coagulation Cascade:**
    - **Thrombomodulin:**
      - Blocks Thrombin from activating Fibrinogen :. No Fibrin Deposition
  - **& By Breaking Down Fibrin:**
    - Via a *Fibrin-Digesting Enzyme:* ***Plasmin*** → Degrades fibrin & :. The clot as well.
      - Plasmin: Produced when ***Plasminogen*** is activated.
      - Plasminogen is initially incorporated into a forming clot → Remains inactive until clot forms.
      - **Plasminogen Activation:** (once clot is formed)
        - **Endothelial Cells:** secrete ***Tissue Plasminogen Activator (tPA)***
        - **Activated Factor XII:** also *Activates Plasminogen*
        - **Thrombin:** also *Activates Plasminogen*
    - Results in Fibrin Degradation Products (FDP's):
      - Can be measured in the blood
      - Tested to see whether there has been excessive blood clotting

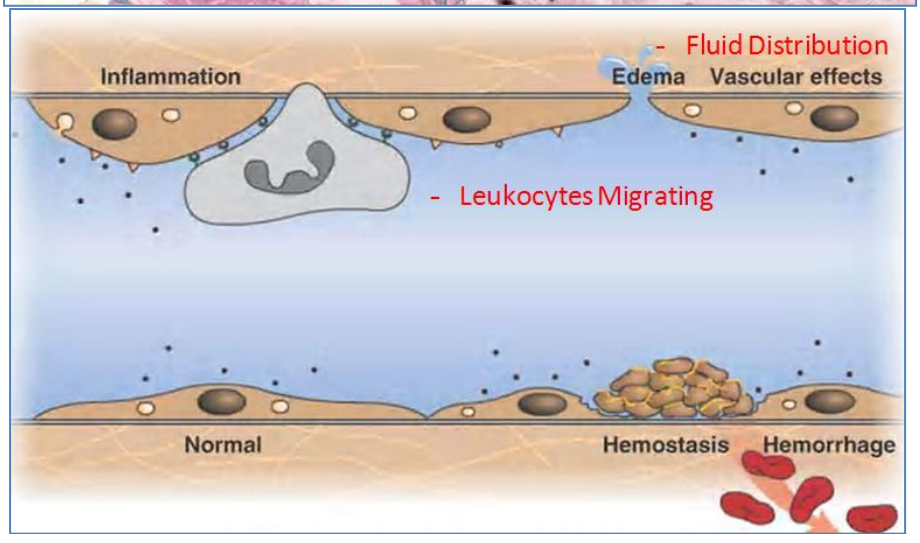
OVERVIEW:



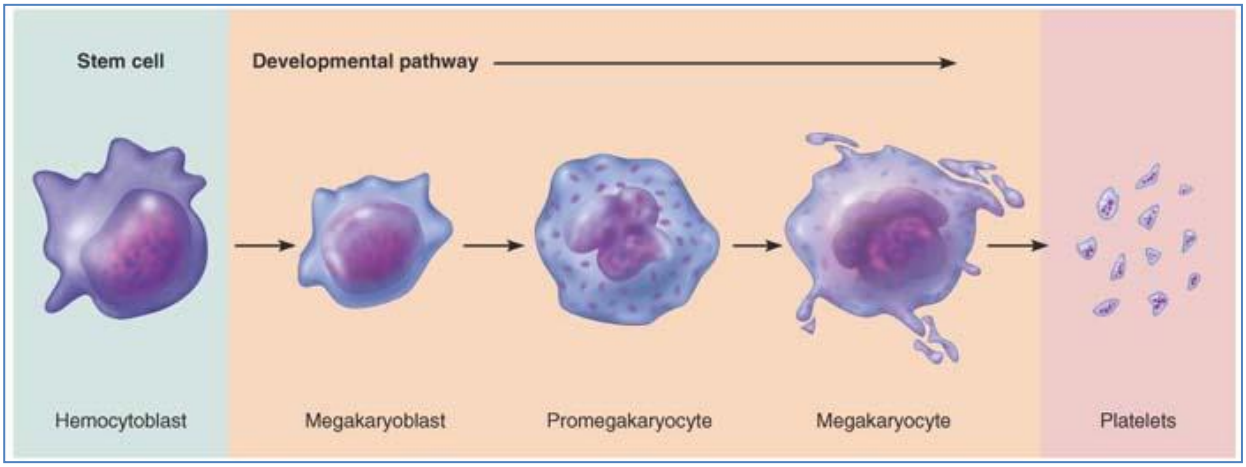
Components of Haemostasis:

- **Endothelial Cells:**
  - Simple Squamous Epithelium
  - Lines the blood vessels
  - Small amount of Smooth Muscle around outside.
  - **Important For:**
    - Barrier between intra/extra vascular tissues
    - Regulate/mediate inflammation – facilitate movement of leukocytes
      - Leukocytes must be able to migrate from intra-extra vascular sites.
    - Fluid Distribution – can change permeability → Fluid (Plasma) can exit to Interstitial Space
    - **Haemostasis:**
      - **Promote Plug Formation & Coagulation when injured**:
        - **Pro-Platelet Effects:**
          - Exposure of SubEndothelial Collagen
          - Produce Von Willebrand Factor (the glue)
        - **Pro-Coagulant Effects:**
          - Exposure of Tissue Factor → Triggers Extrinsic P-way of Coag. Cascade.
        - **Anti-Fibrinolytic Effects:** (pro-fibrin deposition)
          - Blocks the Tissue Plasminogen Activator.
      - **Inhibits Plug Formation & Coagulation when intact**:
        - **Anti-Platelet Effects:**
          - Nitric Oxide
          - & .....
        - **Anti-Coagulant Effects:**
          - Heparin
          - & Thrombomodulin
        - **Fibrinolytic Effects:**
          - Tissue Plasminogen Activator
    - **Angiogenesis**:
      - Formation of new vessels
      - Or Vessel Repair.





- **Platelets:**
  - Produced in bone marrow: From Megakaryocytes
    - Fragment into many platelets
    - 4000 platelets/megakaryocyte
  - Production Stimulated by ***Thrombopoietin*** (produced by Liver & Kidneys)
  - **Functions:**
    - Central role in Haemostasis
    - Form platelet-plugs at vascular injury.



- **Coagulation Cascade:**
  - Role: To stabilise primary platelet plug
  - Protects plug from being washed away by flowing blood
  - Dependant on circulating *plasma proteins* (Coag. Factors)
    - Mainly produced in liver
    - Some severe liver diseases → clotting deficiencies.
- **Fibrinolysis:**
  - Clots aren't permanent solutions to vessel injuries.
  - :. Fibrinolysis removes un-needed clots after healing has occurred...by:
    - Blocking Coagulation Cascade:
    - & By Breaking Down Fibrin:

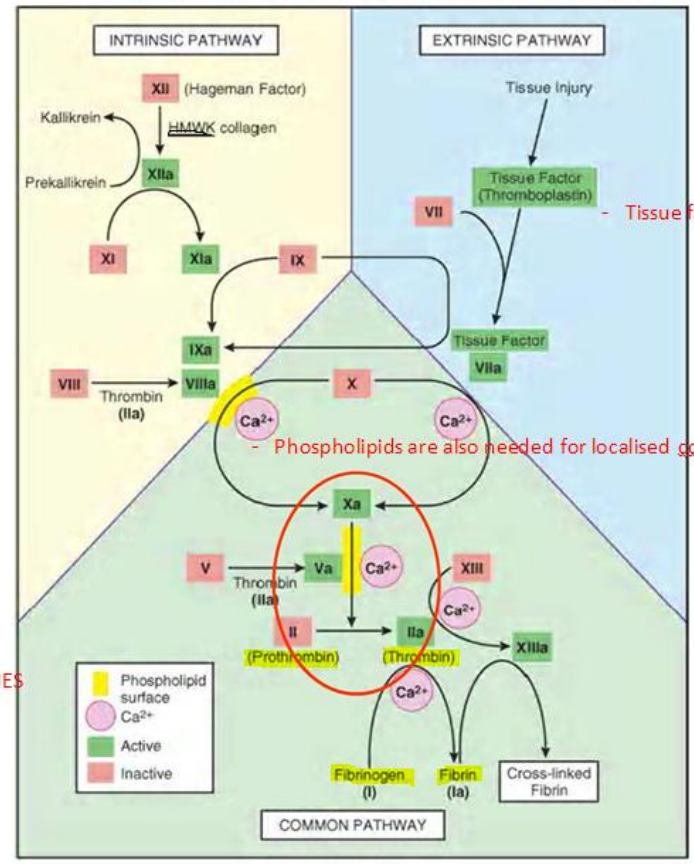
There are different diagnostic tests for intrinsic & extrinsic pathways

Coagulation Factors

I Fibrinogen
II Prothrombin
III Tissue factor
V (Labile factor)
VII (Proconvertin)
VIII Antihaemophillic Factor
IX Christmas factor
X Stuart-Prower factor
XI (Plasma thromboplastin antecedent)
XII Hageman factor
XIII (Fibrin stabilising factor)

DON'T WORRY TOO MUCH ABOUT NAMES

Brackets not too important



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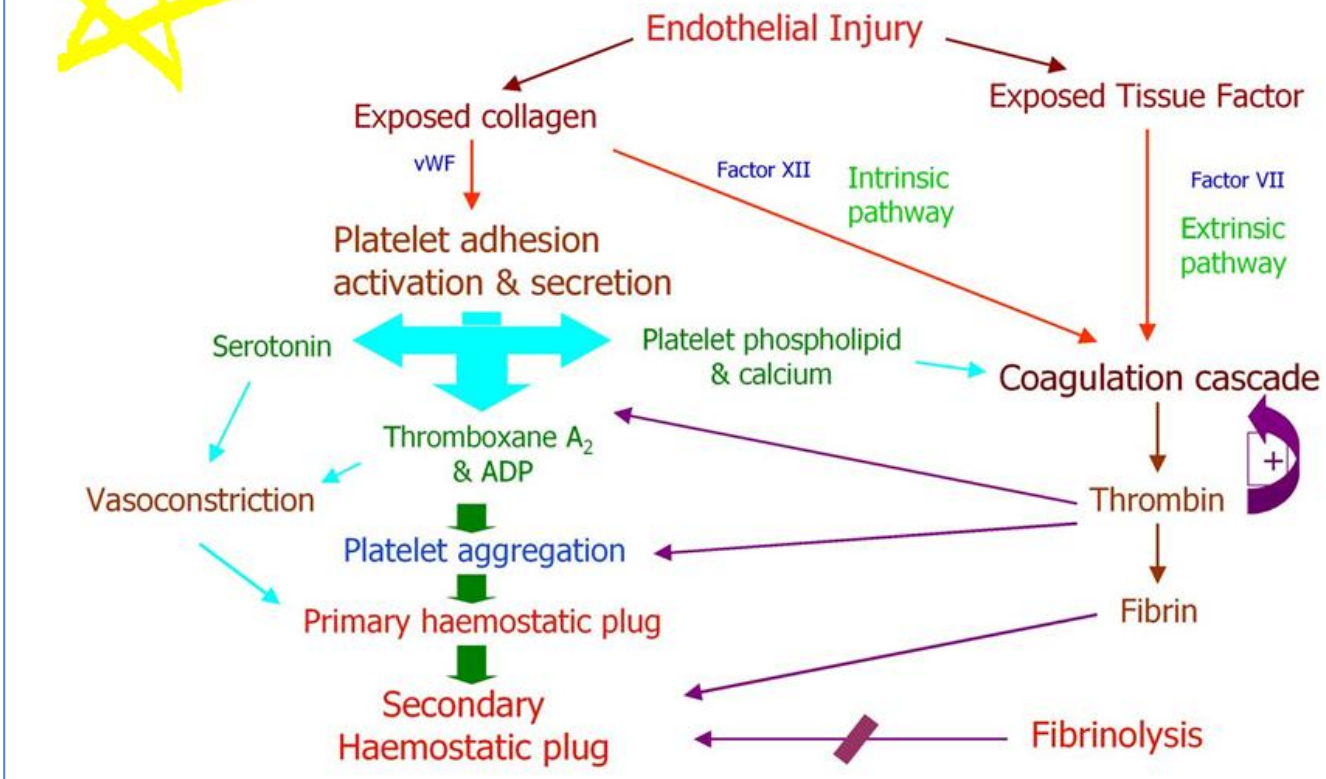
- Tissue factor + Factor 7

Pink = inactive precursors
Green = active

- Phospholipids are also needed for localised coag (yellow)

Overview of Haemostasis



Check out this website.
http://www.mhhe.com/biosci/esp/2002_general/Esp/folder_structure/tr/m1/s7/trm1s7_3.htm

Disorders of Haemostasis

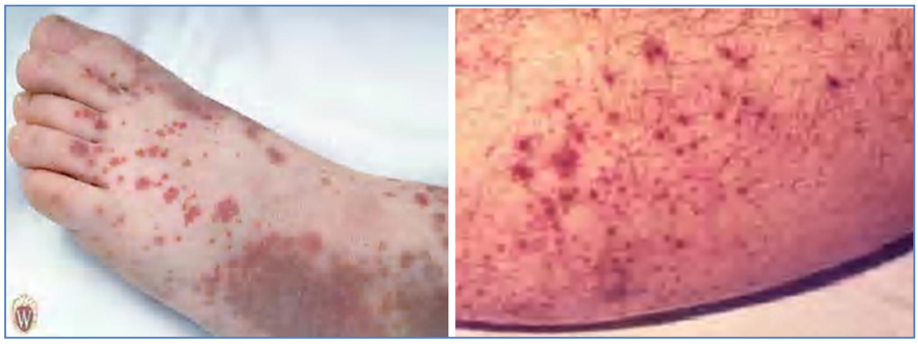
1. Bleeding Disorders:

- **Vascular Disorders:**
  - Abnormalities in Blood Vessel Structure or Perivascular Connective Tissue
  - Leads to: Easy Bruising
    - Can be Petechial ...or
    - Ecchymotic Haemorrhages
  - May be:
    - Inherited:
      - Genetic Mutations
      - Usually Autosomal Recessive
    - Or Acquired:
      - Via Age
      - Bacteria
      - Nutritional (eg. Scurvy)

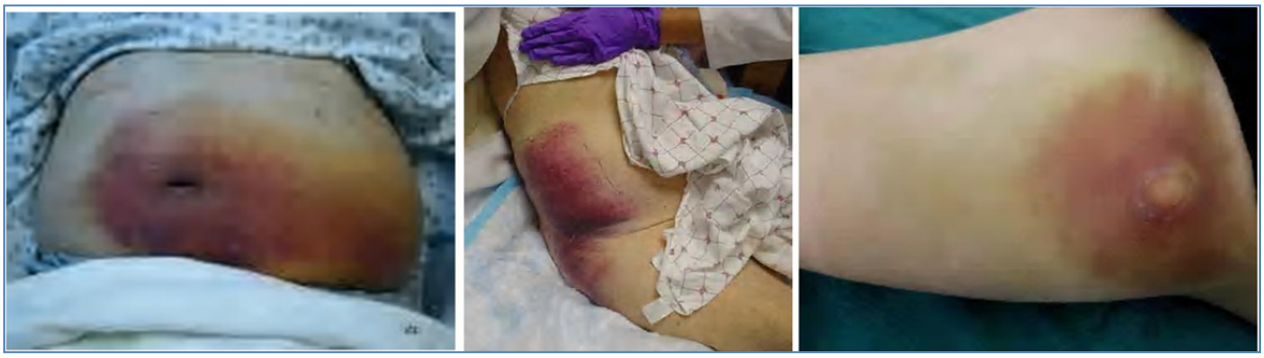
- **Thrombocytopenia, Defective Platelet Function & Von Willebrand's Deficiency:**
  - Often cause Petechial Haemorrhages
  - How?:
    - They all *prevent proper platelet plug formation.*
  - **More specifically:**
    - **Thrombocytopenia:**
      - Due to ***deficient number of platelets.***
      - Results from either:
        - ↓ Platelet Production
        - ↑ Platelet Destruction
        - ↑ Platelet Consumption (in large injuries/burns)

    - **Defective Platelet Function:**
      - There are enough platelets, but not working properly.
      - May be Inherited (rare)...OR
      - Acquired: (eg. From Aspirin/other blood thinners)

    - **Von Willebrand's Deficiency:**
      - Due to Either:
        - Not enough vWF....or
        - Dysfunction of vWF.
      - Ordinarily vWF is necessary for platelet adhesion.
      - :. Deficiency → Poor platelet plug formation



- **Coagulopathy = Defective Coagulation:**
  - Bleeding disorders
  - Results in:
    - Muscle Haematomas
    - Haemarthroses (Bleeding into joint spaces)
    - Excessive Bleeding
  - Due to deficiency in 1 or more Coag. Factors
  - May Be:
    - **Heriditary:**
      - **Haemophilia A: Factor VIII Deficiency:**
        - Most common
        - Sex Linked Recessive (Female Carriers; Affected Males)
      - **Haemophilia B: Factor IX Deficiency:**
        - AKA. Christmas Disease
        - Less common
        - Sex Linked Recessive (only affects males)
      - **Other deficiencies (Factors V, VII, X, XI & XIII) Rare.**
        - Just know they exist.
    - **Acquired:**
      - **Vitamin K Deficiency (Factors II, VII, IX, X)**
        - Due to either:
          - Diet
          - Malabsorption
          - Long-term warfarin
      - **Liver Disease:**
        - Eg. Billiary Obstruction:
          - Hinders absorption of Fat-Soluble vitamins
          - Reduced synthesis of Factors II, VII, IX & X
        - Eg. Severe Hepatocellular Damage:
          - Reduced synthesis of Factor V & Fibrinogen
      - **DIC - Disseminated Intravascular Coagulation:**
        - AKA. Consumptive Coagulopathy
        - Formation of small clots inside blood vessels throughout the body.
        - Leads to: ↑Consumption of Platelets & Coagulation Factors.



1. Evaluation of Haemostasis:

- **Platelet Count**
  - Literally the number of platelets/volume of blood.
  - Normal range = 150-400x10^9/L
  - Excessively Low platelet count → Thrombocytopenia (bleeding disorder)

- **Platelet Function Tests**
  - **Complete Blood Count (CBC)/Full Blood Evaluation (FBE):**
    - Include platelet count & morphology.- eg. Giant platelets
  - **Bleeding Time**
    - Time taken for wound to clot
    - If bleeding time is high → may suggest platelet dysfunction.
    - If bleeding time is high, *but normal platelet level* → May be due to vWF Deficiency.
  - **Platelet Aggregometry:**
    - Measures platelet aggregation with common haemostatic agonists
      - ADP
      - Epinephrine
      - Collagen
    - Measures the decrease in optical density that occurs in solution as platelets aggregate.

- **Tests of Coagulation-Factor Function:**
  - **Prothrombin Time (PT):**
    - *Time taken for plasma to clot after addition of tissue factor (Factor III)*
    - Measures *Extrinsic Pathway* + part of *Common Pathway*
    - Measures factors VII, X, V, II (Prothrombin) and I (fibrinogen).
    - Normally 12-15sec.
    - 15sec+ = One/more of above factors are deficient.
    - INR (International Normalized Ratio) is derived from PT → Universal measurement.
  - **Activated Partial Thromboplastin Time (aPTT):**
    - *Time taken for plasma to clot after addition of phospholipids*
    - Measures *Intrinsic Pathway* + the *Common Pathway*
    - Measures factors XII, XI, IX, VIII, X, V, II (Prothrombin) and I (fibrinogen).
    - Normally 25-45sec.
    - 45sec+ = One/more of above factors are deficient.
  - **Thrombin Time:**
    - Measures how quickly Thrombin is being activated.
    - Time taken for a clot to form, following addition of animal Thrombin.
    - Measures:
      - The conversion of Fibrinogen → Fibrin.
      - Any deficiency of fibrinogen
      - Any inhibition of thrombin.

Know these 2 evaluation tests:

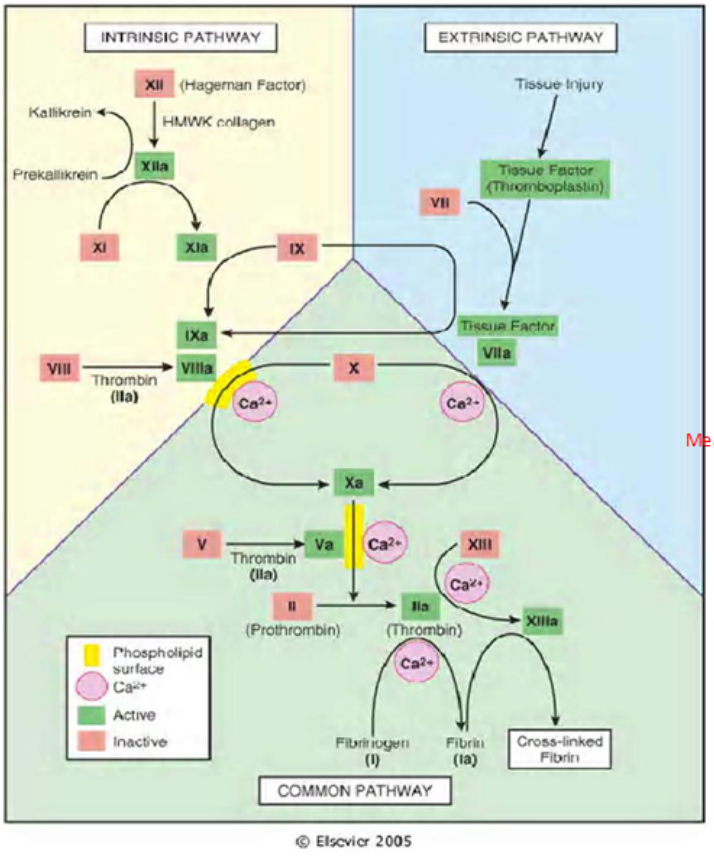
Localising which pathway/which factors are deficient.

Coagulopathy: Deficiency in Coagulation Factor(s)

If: Only aPTT prolonged:

Means: deficient in Factor VIII, IX, XI or XII,

(Factor 12 deficiency isn't a problem)



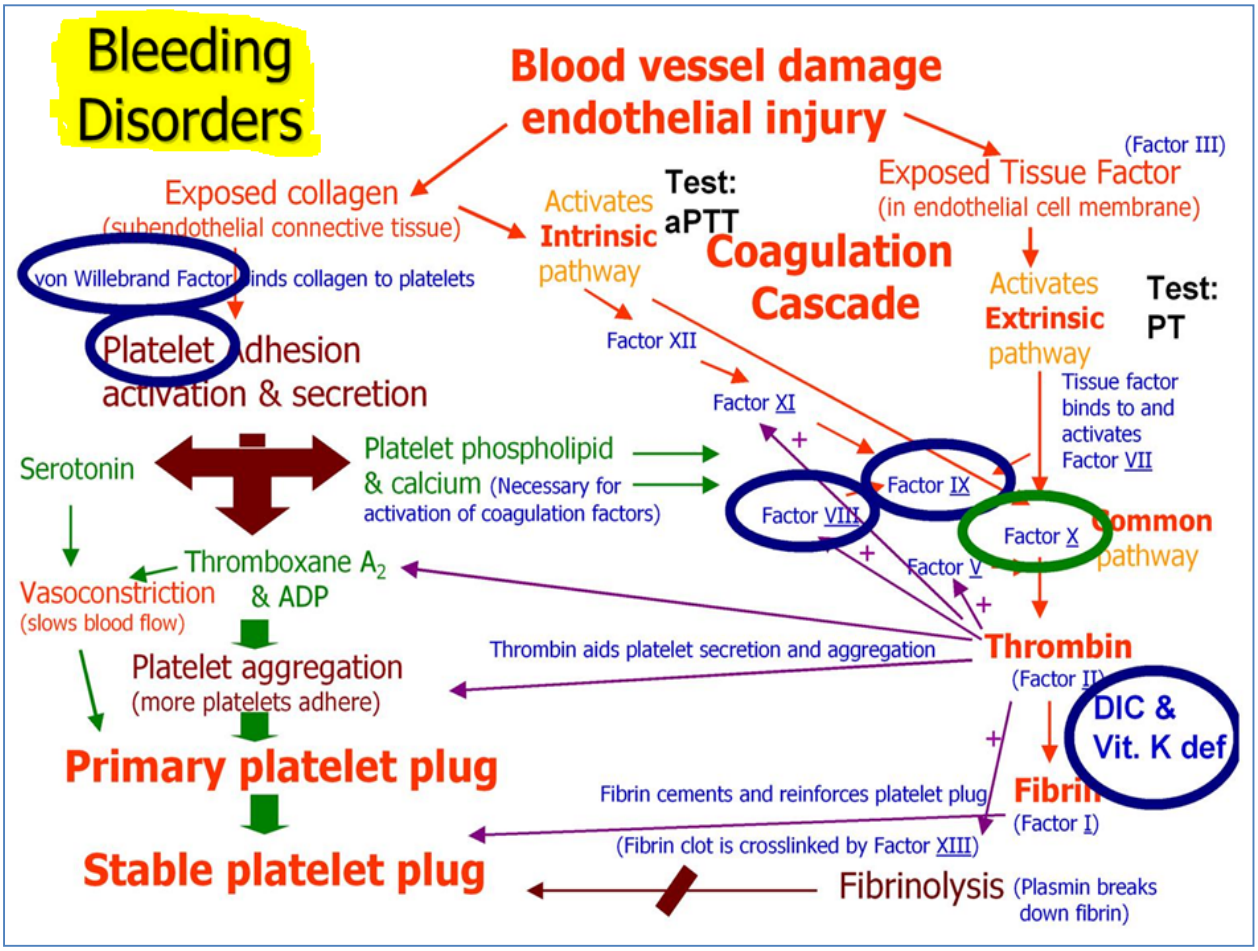
If: Only PT prolonged:

Means: deficient in Factor VII

If: Both PT & aPTT prolonged:

Means deficient in a Factor within the common pathway: (Factor X, V, II or I) OR multiple Factors affecting both pathways- Eg. Liver disease/vitamin deficiency/etc etc.

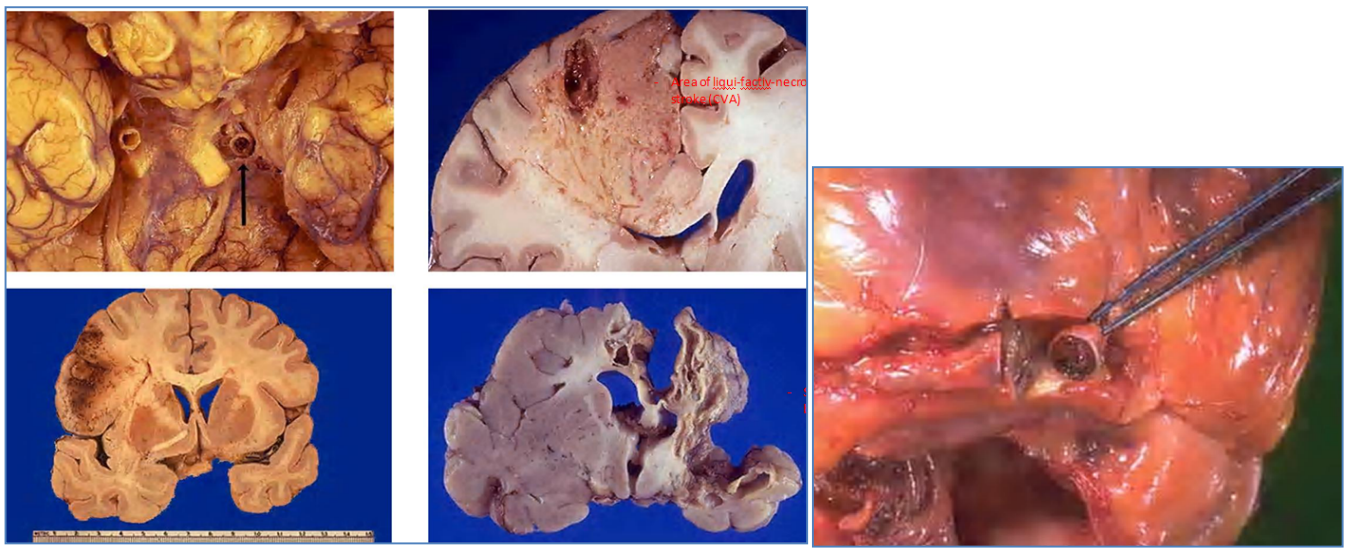
NB: Once the defective pathway is identified, there are other tests for specific factors to help narrow it down.



2. Thrombotic Disorders:

- NB: Thrombosis = inappropriate formation of Platelet & Fibrin Clots
  - Can cause obstruction to flow → Ischaemia → Necrosis
  - **Can Move Elsewhere = "*ThromboEmbolism*":**
    - Most are asymptomatic
    - Fragments move swiftly in large vessels
    - Lodge in small vessels – eg. Pulmonary Vessels → Ischaemia/Necrosis of Lung Tissue.
      - 95% of *Pulmonary Emboli* – due to Thrombosis of Leg/Calf muscles.
  - More common with ↑age
  - Affects both Arterial & Venous Systems

- **Arterial Thrombosis:**
  - **Atherosclerotic Plaque in Arterial walls → Arterial Thrombosis.**
    - Ie. Rupture of Atherosclerotic Plaque →
      - Exposure of SubEndothelial Collagen
      - Exposure of Tissue Factor
  - **Risk Factors:**
    - Family Hx
    - Males (more common)
    - ↑Cholesterol
    - Diabetes
    - ↑BP
    - Smoking
    - Obesity
    - Age
  - **Most common cause of:**
    - **CerebroVascular Accidents (CVA's)** – aka. Stroke – Clot in brain → Necrosis of Neurons
    - **Myocardial Infarction (MI)** – Due to Thrombi related to atherosclerosis in Coronary Arteries → Necrosis of Myocardium
    - **Peripheral Arterial Disease (PAD)**



- **Venous Thrombosis:**
  - Very Rare (Affects 1/1000 people)
  - Occur Mostly in Lower Extremities (due to gravity pooling blood)
    - Includes Deep & Superficial Leg Veins
      - Iliac
      - Popliteal
      - Femoral
    - Patient may present with sore or swollen legs/calves.
  - Less Common in Upper Extremities/Abdominal Organs/Brain
  - **Risk Factors:**
    - **Heriditary**:
      - Factor V mutation
      - Prothrombin variant
      - Protein C deficiency
      - Protein S deficiency
      - Antithrombin Deficiency

    - **Acquired Hypercoagulable States:**
      - **High-Dose Oestrogen Therapy:**
        - ↑Plasma levels of Coag. Factors
        - ↓ Antithrombin & Tissue-Plasminogen-Activator

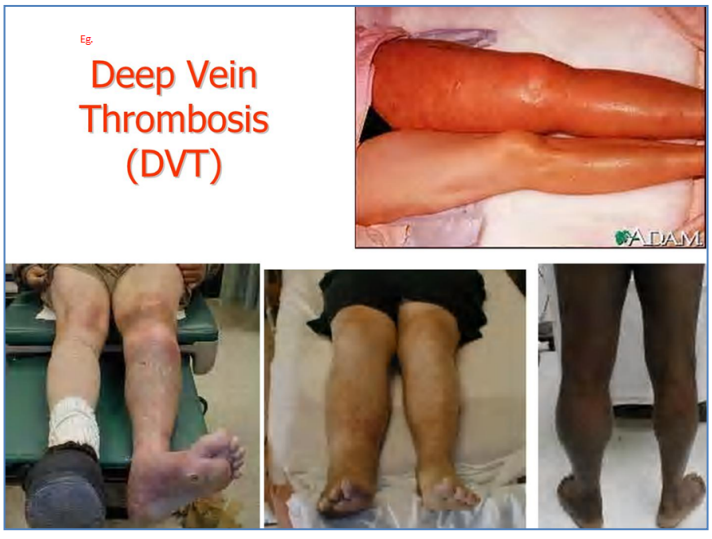
      - **Major Surgery/Trauma:**
        - Due to high tissue damage
        - Immobility after surgery (Venous Stasis)
        - Exposure of Tissue Factor

      - **Pregnancy & Post-Partum (↑Levels of Coag. Factors during pregnancy)**

      - **Sepsis (bacterial infection → widespread damage to endothelium)**

      - **Heparin-Induced Thrombocytopaenia** (some people on heparin develop antibodies to their own platelets)

      - **Blood Stasis**:.....from:
        - Heart Failure (not pumping adequately)
        - Stroke
        - Prolonged Immobility
        - Nephrotic Syndrome (loss of Coag. Factors through Urine)
        - Varicose Veins



2. Evaluation of Thrombosis:

- Required if:
  - Family History of Thrombosis
  - Thrombosis at young age/unusual site
  - Recurrent DVT

- **Complete Blood Count ...&...Erythrocyte Sedimentation Rate:**...Detect:
  - Change in Haematocrit
  - Change in White Cell Count
  - Change in Platelet Count
  - Change in Fibrinogen
  - Red Cell Fragmentation

- **Prothrombin Time (PT):**
  - *Time taken for plasma to clot after addition of tissue factor (Factor III)*
  - See above section for details.
  - *Detects deficiency of Factor VII*

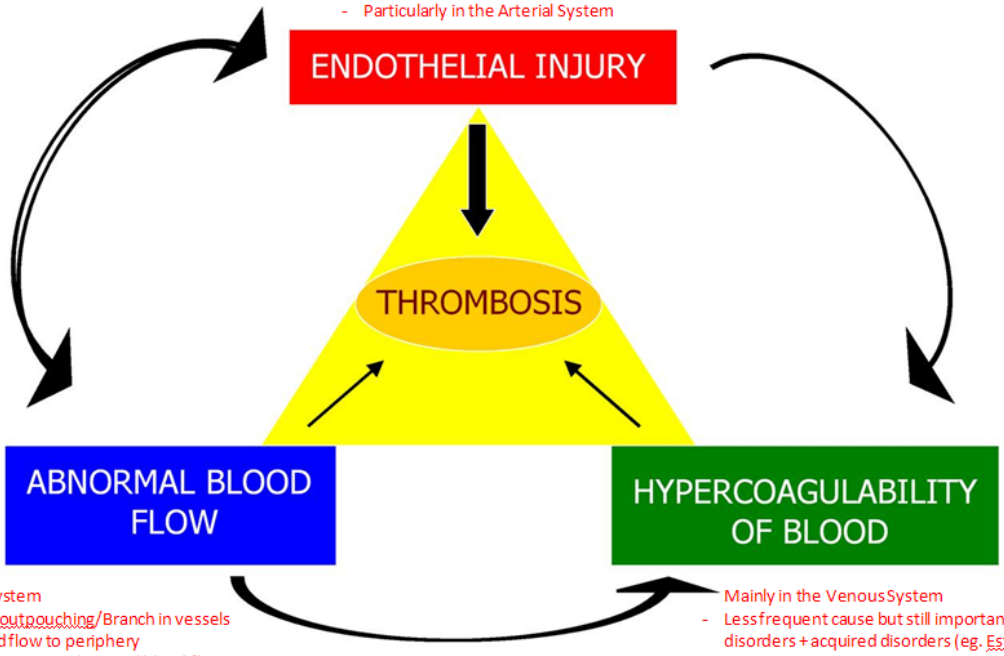
- **Activated Partial Thromboplastin Time (aPTT):**
  - *Time taken for plasma to clot after addition of phospholipids*
  - See above section for details.
  - *Detects deficiency of Factors VIII, IX, XI or XII.*

- **If *Both* PT & aPTT are Abnormal:**
  - *Probably due to:*
    - *Liver disease*
    - *Vit. K Deficiency……..or*
    - *Oral Anticoagulants*

Pathogenesis of Thrombosis

Virchow Triad

- Particularly in the Arterial System



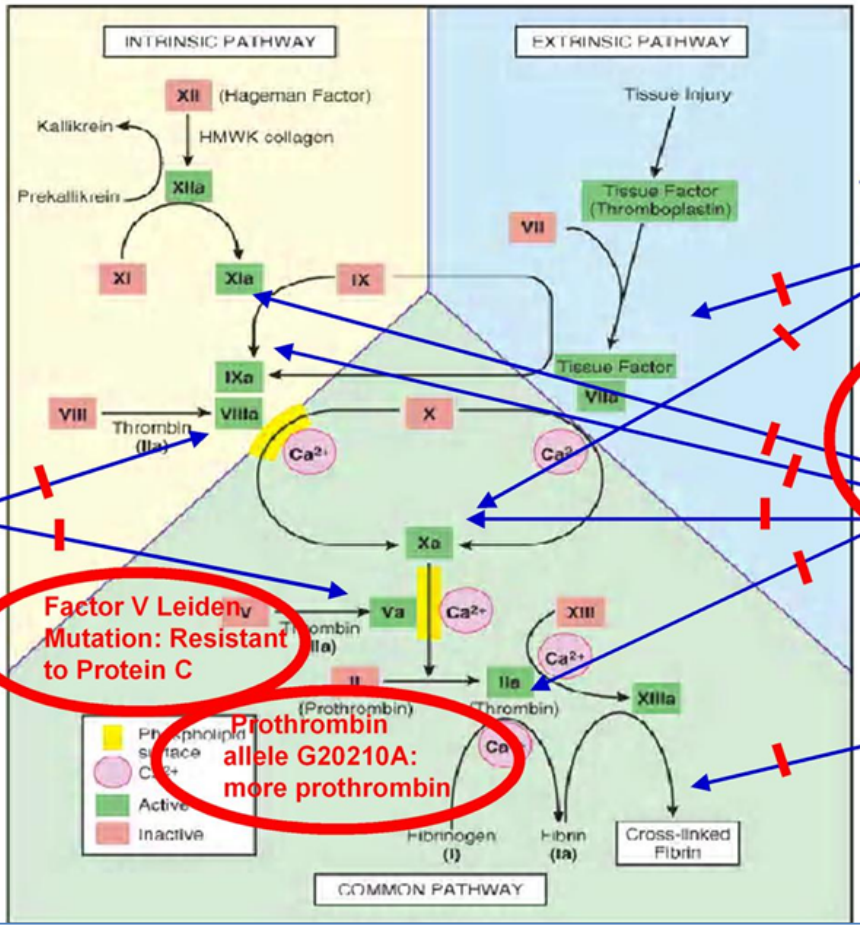
Mainly in the Venous System
Eg. Turbulance - Due to outpouching/Branch in vessels
Eg. Stasis - Slowed blood flow to periphery
Endothelial injury can also cause abnormal blood flow

Mainly in the Venous System
- Less frequent cause but still important - particularly in genetic disorders + acquired disorders (eg. Estrogen therapy can increase coagulability)

Thrombotic Disorders

test: aPTT

test: PT



Thrombin binds to thrombomodulin in endothelium

Activates Protein C + Protein S

Protein C or protein S deficiency: more factor V & VIII

Factor V Leiden Mutation: Resistant to Protein C

Prothrombin allele G20210A: more prothrombin

Tissue Factor Pathway Inhibitor inactivates TF-VII complex and X

Antithrombin deficiency: more factors IX, X, XI & II

Antithrombin III + Heparin inactivates IX, X, XI and thrombin (II)

Plasmin degrades fibrin

Tissue Plasminogen Activator

The Main 2 AntiCoagulant Drugs:

- **Heparin (INJECTABLE):**
  - Fast-acting
  - How?: Stimulates Antithrombin Activity
  - 2 Types:
    - Standard Heparin:
      - Rapid Action
      - Initially administered by IV, then SubCutaneously.
      - Monitored by aPTT
    - Low Molecular-Weight Heparin:
      - Slower Action
      - But Longer Half-Life
      - Not Monitored by aPTT
- **Warfarin (ORAL):**
  - Most common oral Coag.
  - How?: Vitamin K Antagonist (Decreases Factors II, VII, IX & X)
  - Is Teratogenic
  - Can Cross Placenta
  - Monitored by PT

Fibrinolytic Drugs:

- Degrade Thrombi
- Used Systemically...or...injected directly into thrombus.

Antiplatelet Drugs:

- Eg. Aspirin:
  - Reduces Thromboxane A_2 Production
  - Reduces Platelet Aggregation
  - Often used in patients with Atherosclerosis → Prevents Thrombi.

GLS STUFF:

Thrombotic Disorders

Factor V Leiden Mutation (resistance to Protein C)
Autosomal dominant. 4-6% population. Abnormal Factor V is not broken down in bloodstream by Protein C. Increased risk of venous thrombosis. Heterozygous 5-8 fold, homozygous 30-140 fold increase. Signs: Variable, recurrent thrombosis <30yrs, DVT, PE. Diag: Activated protein C resistance (Failure to have increased aPTT time with added protein C), PCR for the mutation. Treat: heparin or warfarin if thrombosis occurs.

Prothrombin allelle G20210A
Autosomal dominant. 2-3% in pop. Increased prothrombin. Increased risk thrombosis. Signs: DVT, pulmonary embolism, CVA. Diag: PCR of prothrombin, prothrombin levels. Treat: anticoagulants eg heparin, warfarin, aspirin.

Antithrombin Deficiency
Autosomal dominant. Deficiency or dysfunction of Antithrombin III (which inhibits thrombin, Factor X and Factor IX). Signs: Recurrent venous thrombosis early in life, DVT, PE. Occ arterial thrombi. Diag: Antithrombin activity tests. Treat: anticoagulants, antithrombin concentrates esp if surgery or childbirth.

Protein C Deficiency
Autosomal dominant. Increased risk thrombosis. Protein C degrades coagulation Factors eg V and VIII (after activation by thrombin/thrombomodulin) and enhances fibrinolysis. Enhanced by Protein S. Vit K dependent. Signs: Increased risk thrombosis, DVT, embolism. Skin necrosis from vessel occlusion if warfarin therapy because reduced Protein C before reduced K-dependent clotting factors. Treat: anticoagulants, Protein C concentrates.

Protein S Deficiency
Autosomal dominant. Vit K dependent. Is a cofactor for Protein C, binds protein C to platelet surface. Features similar to Protein C deficiency. Signs: Increased risk thrombosis, DVT, embolism. Risk skin necrosis with warfarin therapy. Diag: Protein S antigen, protein S functional activity. Treat: anticoagulants eg heparin, warfarin.

Combined Bleeding & Thrombotic Disorder

Disseminated Intravascular Coagulation
Secondary to severe disease, many systemic causes (sepsis, burns, trauma, malignancy etc). Widespread endothelial & tissue damage & exposure tissue factor causes activation of coagulation (multiple micro-thrombosis) and consumption of coagulation factors and platelets which leads to bleeding. Signs: thrombosis, embolism, haemorrhage. Diag: low platelets, low fibrinogen, prolonged Thrombin time, high FDPs eg D-dimer test, PT and aPTT may be prolonged, red cell fragmentation. Treat: underlying cause, fresh plasma, cryoprecipitate, heparin etc.

Bleeding Disorders

Haemophilia A

Sex-linked recessive. Deficient Factor VIII. 30-100 per million of population. Signs: Severe bleeding in males. Haemarthrosis, muscle haematomas, prolonged bleeding after minor trauma. Diag: Prolonged aPTT, abnormal Factor VIII clotting assay. Normal PT and bleeding time. Prenatal diagnosis if carrier mother. Treat with Factor VIII eg tri-weekly, or desmopressin if mild.

Factor IX deficiency (Christmas, Haemophilia B)

Sex-linked recessive. Deficient Factor IX (Vit K dependent Factor). Signs: Variable severe bleeding in males. Same clinical signs as Haemophilia A, 1/5 as common as Haemophilia A. Vit K dependent Factor. Diag: Prolonged aPTT, Factor IX assay. Treat with Factor IX concentrates, longer half life so less frequent treat than A.

Factor X Deficiency (Stuart-Prower)

Autosomal recessive. Rare. Deficient or abnormal Factor X function. Vit K dependent. Activated Factor X required to activate prothrombin to thrombin. Signs: Variable bleeding. Haemarthrosis, haematomas. Diag: Prolonged PT and aPTT, Reduced Factor X antigen and activity. Treat: plasma, Prothrombin complex concentrates (II, VII, IX, X), vit K if deficient.

Von Willebrand Disease

Common. Family of disorders (Type 1,2,3). Usually autosomal dominant with variable expression. Reduced amount or abnormal function of vWF. (vWF promotes platelet adhesion to collagen and carries and protects Factor VIII). Signs: Variable severity of bleeding. Epistaxis, menorrhagia, post-trauma bleeding, bruising. Diag: Prolonged bleeding time, often low levels Factor VIII (aPTT may be prolonged), may be low levels vWF, may be defective platelet function in presence of ristocetin, normal platelets. Treat: desmopression for type 1, high purity vWF if low levels, Factor VIII concentrates.

Thrombocytopenia

Common. Abnormally low number of platelets: Decreased production (eg bone marrow disorder, radiation, toxins), decreased survival (immune, idiopathic, infection eg HIV, drugs, transfusions), sequestered (splenomegaly). Signs: petechia, epistaxis, gum bleeding, menorrhagia. Diag: platelet count, marrow aspirate. Treat: corticosteroids if immune, treat underlying cause, splenectomy, transfusion.

Vitamin K Deficiency

Fat soluble vitamin from green veges and bacteria in gut. Decreased activity of Factors II, VII, IX, X, protein C, protein S. More common in newborn, malnutrition, malabsorption, warfarin therapy. Signs: epistaxis, bleeding, bruising, haemarthrosis. Diag: Prolonged PT and aPTT. Treat with Vit K supplemetation.

Clinical Pharmacology & Toxicology Notes
Drugs for Haemostasis

REVISION OF HAEMOSTASIS:

- **Purpose of Haemostasis:**
  - To Stop blood loss from Damaged Vessels
- **Factors Involved – (Those in red are targeted by different Drugs to modulate Haemostasis):**
  - **Platelet Aggregating Agents:**
    - Sub-Endothelial Collagen (activates Platelets)
    - **Thromboxane** (Stimulates Expression of Glycoprotein Receptor "GP-IIb/IIIa" → Aggregation)
      - (Produced by Cyclo-Oxygenase in Platelets)
    - **ADP** (Stimulates activation of Glycoprotein Receptor "GP-IIb/IIIa" → Platelet-Aggregation)
    - **Glycoprotein Receptor "GP-IIb/IIIa"** – Allow platelets to *physically combine* with each other.
      - Promoted by ADP Receptor Activation.
  - **Anti-Platelet-Aggregating Factors:**
    - **↑cAMP**→↑cAMP Inhibits Platelet Aggregation by **decreasing Cytosolic Ca^+ Levels**.
      - ↓Ca^+ → **Inhibits Ca-Mediated Vesicular Exocytosis of Pro-Aggregation Factors** from the Platelet (Particularly Thromboxane).
  - **Pro-Coagulating Agents:**
    - **Vitamin K** (A Coenzyme in the synthesis of Prothrombin, Factors II, VII, IX & X (TV Channels)
    - Coagulation Factors I-XIII
    - Activated **Factor X** (Complex)
    - Prothrombin → **Thrombin** (Factor II)
    - Fibrinogen → Fibrin
  - **Anti-Coagulating Agents (In Non-Damaged Tissue):**
    - **Antithrombin-III** (Inactivates Thrombin {Factor II}→ ~~Fibrinogen Activation~~ →~~Fibrin~~)
  - **Fibrinolysis Factors:**
    - Tissue **Plasminogen Activator** → Activates Plasminogen to become Plasmin
    - (Plasmin degrades fibrin clots)
- **PROBLEM: If Haemostasis is *Unregulated*, it can be FATAL!! (Major Haemorrhage/Thrombosis).**

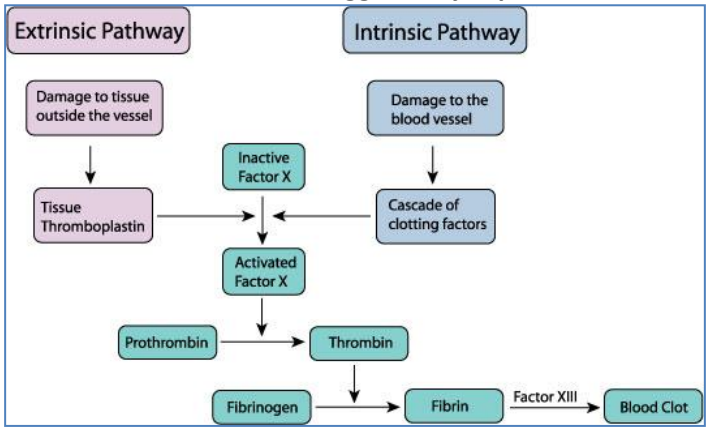
3 Phases of Haemostasis:

- **1. Primary Haemostasis:**
  - **Primary Platelet Plug Formation:**
    - When vessel is damaged → ***Sub-Endothelial Collagen*** is exposed....
      - Platelets **(*+ Von Willebrand Factor*** [glue]**)** adhere strongly to the Collagen Fibres...
      - Primary Platelet-Plug 'Sandwich':

        Surface Glycoproteins on Platelets
        Von Willebrand Factor
        Sub-Endothelial Collagen

  - **Platelet Aggregation:**
    - Once attached, Platelets → Activated → ***Release Several Chemicals:***
      - **GP-IIb/IIIa:** Form the basis of the 'bridge' between platelets.
      - **Thromboxane A_2:** Stimulates GP-IIb/IIIa Expression on Platelets.
      - **ADP:** Activates GP-IIb/IIIa → Enabling aggregation.
      - **Calcium (Factor IV):** A cofactor that *Activates* other *Inactive Pro-Coagulation Factors*.
    - Initiates a Positive Feedback Cycle → Activates & Attracts more & more Platelets.
      - Within 1min, a platelet plug is built → further reduces blood loss.
  - **Platelet-Plug Localisation:**
    - **Prostacyclin:**
      - A Prostaglandin Produced by *Intact* Endothelial Cells.
      - A Strong *Inhibitor* of Platelet Aggregation

- **2. Secondary Haemostasis:**
  - **Coagulation Cascade:**
    - Coagulation (i.e. Blood 'Clotting'): Where Blood; Liquid → Gel
    - Series of enzymatic conversions of *Inactive Coag. Factors* → *Active Coag. Factors.*
    - **Intrinsic Pathway:**
      - →**Triggered by Exposed Sub-Endothelial Collagen**
      - All factors needed for clotting are in the blood
    - **Extrinsic Pathway:**
      - →**Triggered by Exposed Tissue Factor** (Factor III)



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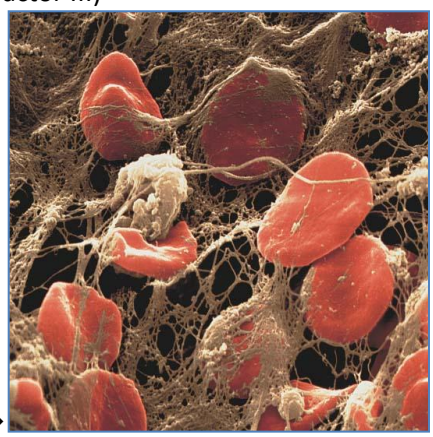
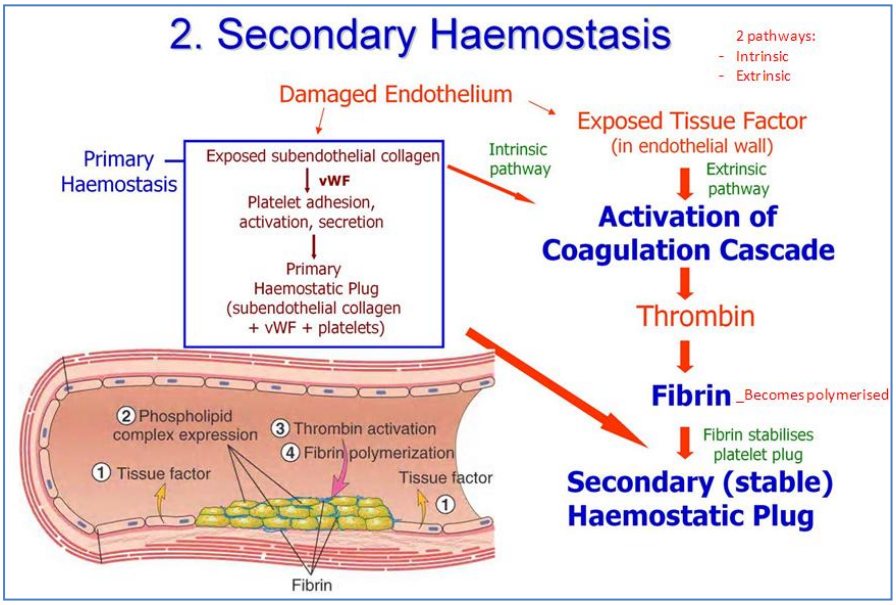
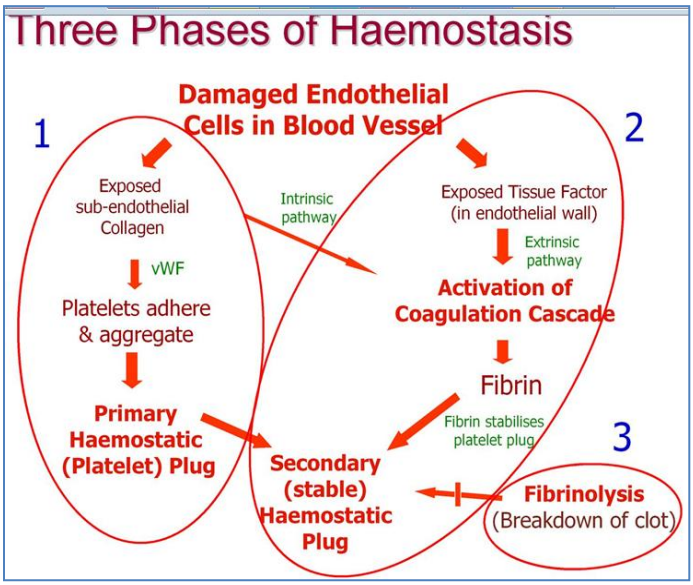


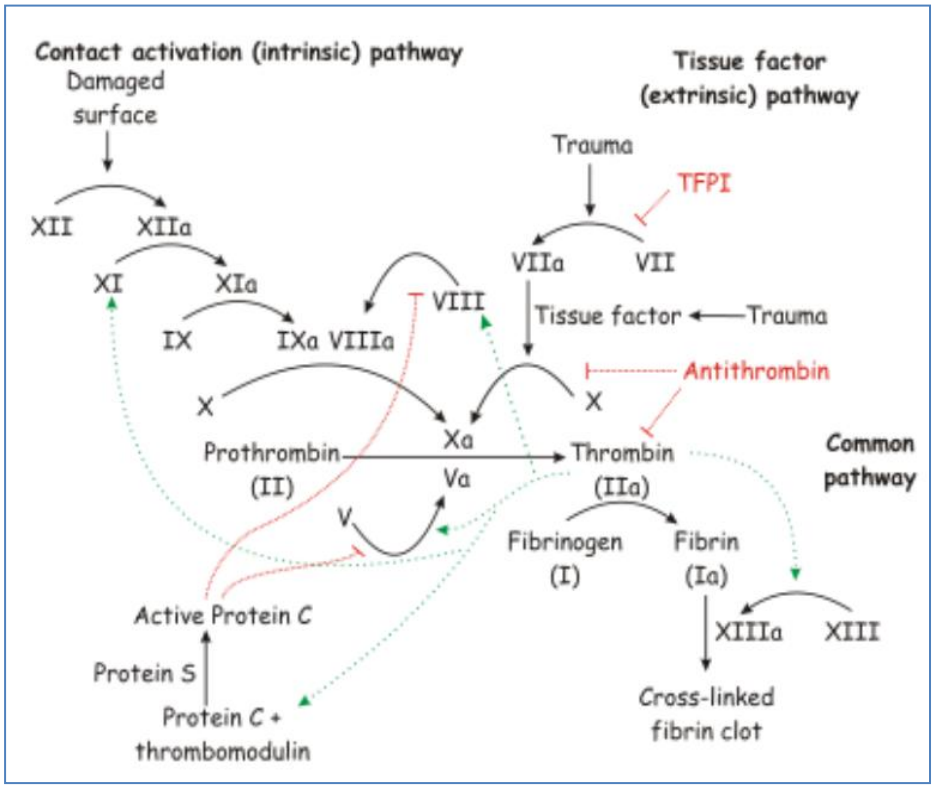
    - Both Pathways eventually lead to ***Activation of Factor-X***
      - **Activated Factor-X** combines with other factors to form→
      - **Prothrombin Activator**→ converts the plasma-protein: ***Prothrombin → Thrombin*.**
  - **Fibrin Deposition:**
    - **Thrombin** Catalyses Conversion & Deposition of ***Fibrinogen →Fibrin***
    - **Fibrin** Mesh →+ ***Active Factor-XIII*** → Stabilises the Platelet-Plug → Seals the hole
      - **Primary Platelet Plug** + *Mesh* → **Secondary Platelet Plug.**
  - **Regulation:**
    - **Pro-Coagulating Agents:**
      - **Vitamin K** (A Coenzyme in the synthesis of Prothrombin, Factors II (Thrombin), VII, IX & X (TV Channels)
      - Coagulation Factors I-XIII
      - Activated **Factor X** (Complex)
      - Prothrombin → **Thrombin**
      - Fibrinogen → Fibrin
    - **Anti-Coagulating Agents (In Non-Damaged Tissue):**
      - **Antithrombin-III** (Inactivates Thrombin → ~~Fibrinogen Activation~~ →~~Fibrin~~



- **3. Fibrinolysis:**
  - Thrombi aren't permanent solutions to vessel injuries.
  - :. Fibrinolysis removes un-needed thrombi after healing has occurred...by:
  - **By Breaking Down Fibrin:**
    - ***Plasminogen Activator*** (Incorporated into a forming clot, but dormant until after healing)
      - **→ Activates *Plasminogen* → *Plasmin*.**
    - ***Plasmin*** → Degrades fibrin & :. The thrombus as well.

OVERVIEW:





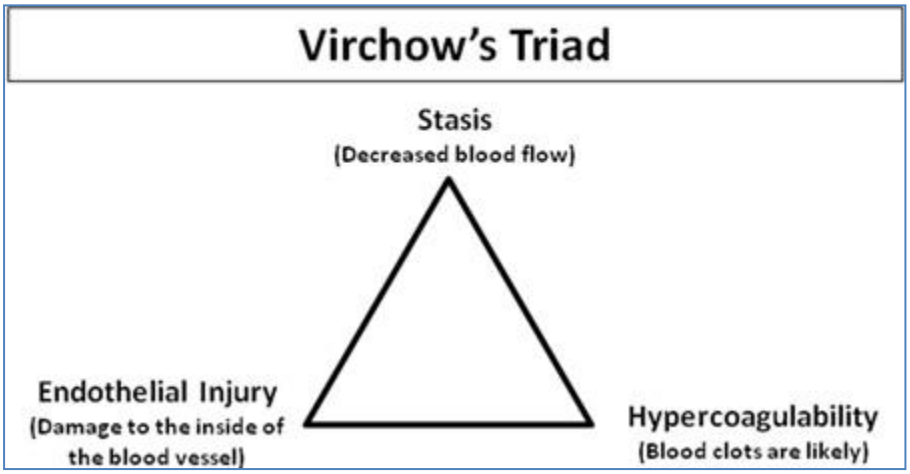
PATHOLOGY OF HAEMOSTASIS:

A "Clot" is Different to a "Thrombus":

- **Clot:**
  - Occurs In-Vitro (Ie. Outside the Body)
  - Also structurally different.
- **Thrombus:**
  - Occurs In-Vivo (Ie. Inside the Body – Typically forms in *moving blood*)
  - Also structurally different.

Virchow's Triad: – Formation of Thrombosis:

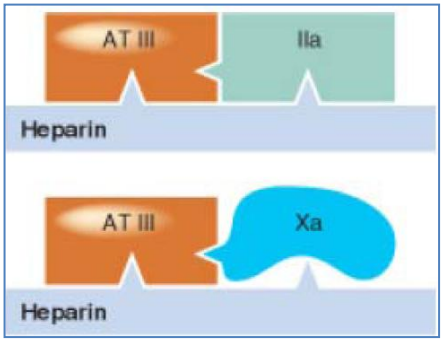
- **Three Conditions Predispose to Inappropriate Thrombus Formation:**
  - **1. Endothelial Injury:**
    - Eg. Atherosclerosis
    - Eg. Aneurysm
    - Eg. Blood Vessel Disorders (Eg. Heriditary Haemorrhagic Telangiactasia)
  - **2. Decreased Bloodflow (Or Stasis):**
    - Eg. Atrial Fibrillation
    - Eg. Deep Vein Thrombosis
    - Eg. Incompetent Venous Valves
  - **3. Hyper-Coagulability:**
    - Eg. During Pregnancy
    - Eg. Drug Side Effects
    - Eg. Hyperproliferative Blood Conditions (eg. Polycythemia Vera)

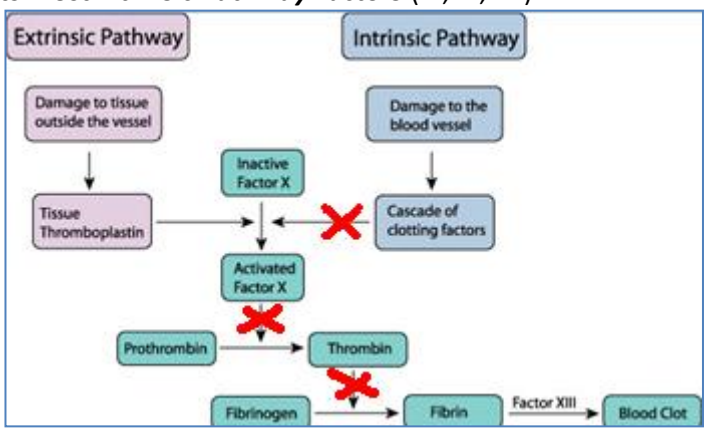


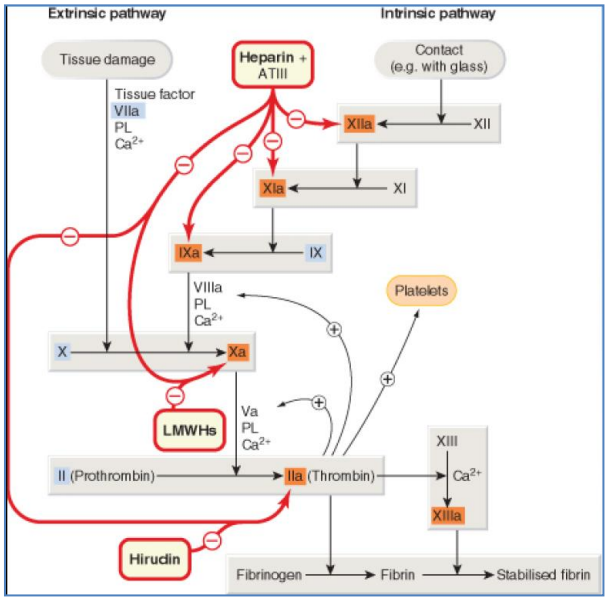
DRUGS FOR HAEMOSTASIS:

ANTI-COAGULANTS: (NB. NOT BLOOD THINNERS!! (In an Exam you'll get ZERO)):

- **Heparin (Including Low Molecular-Weight Heparins):**
  - **Mechanism of Action:**
    - Binds & Activates ***Antithrombin-III*** to form an ***AT-III:Heparin Complex***.
    - The ***AT-III:Heparin Complex*** →**:**
      - 1. → **Inactivates Thrombin (Factor-II):**
        - Therefore Inhibits activation of Prothrombin to Thrombin.
      - 2. → **Inactivates Factor-X:**
        - Therefore Inhibits activation of Fibrinogen to Fibrin.
      - 3. →**Also Inhibits Most *Intrinsic Pathway Factors*** (IX, XI, XII).





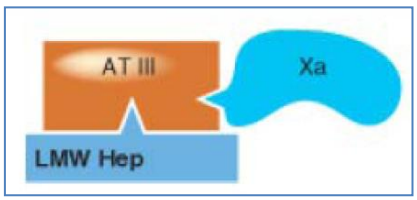


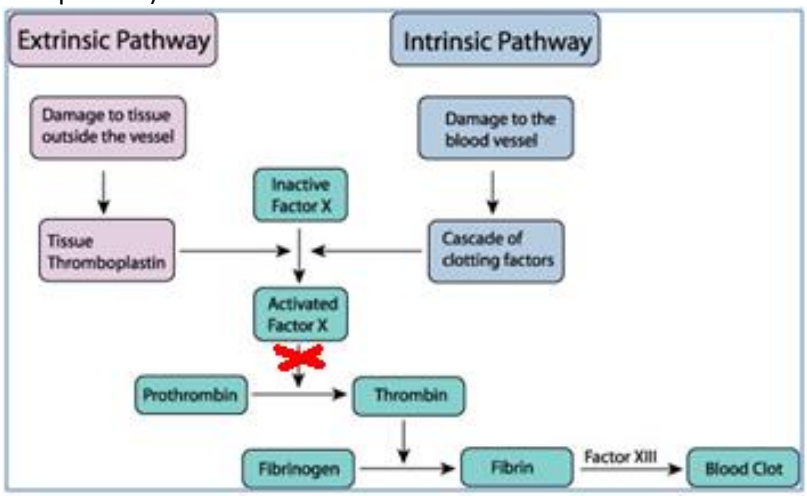
  - **Indications:**
    - Any Acute Coronary Syndrome (eg. NSTE-MI/Unstable Angina/Peripheral Arterial Occlusion)
    - Atrial Fibrillation
    - Deep-Vein Thrombosis & Pulmonary Embolism
    - Heart Surgery
  - **Side Effects:**
    - *Haemorrhage – (However ***Protamine*** is an antidote)
    - *Thrombocytopaenia – (See Next Page)
    - (Osteoporosis)
    - (Hypoaldosteronism with Hyperkalaemi)
    - (Allergic Reactions/Local Reactions – Skin Necrosis, Irritation, Haematomas)
  - **Other Info:**
    - **Rapid (Almost Instant) Onset** of Action
    - Heparin is ONLY used in a *Clinical Setting* (Ie. Pts can't be sent home on it)
    - Cannot be administered orally (too lipophobic → Poor absorption).
      - Therefore Delivered IV → MUST BE MONITORED.

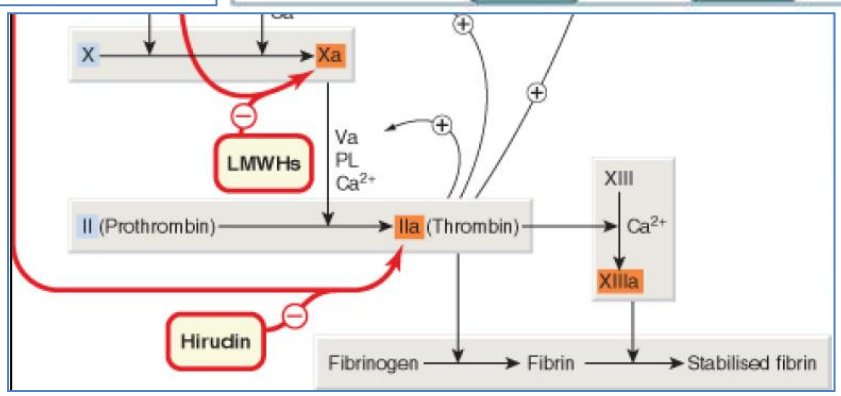
GLS Question: *What is Heparin-Induced Thrombocytopaenia?:*

- ***Thrombocytopaenia – *As a Side-Effect of Heparin*:**
  - **What is Thrombocytopaenia?**
    - Thrombocytopaenia = Low number of Platelets
  - **What is *Heparin-Induced* Thrombocytopaenia?**
    - **Type-I:**
      - Occurs during the first 1-2days of Treatment
      - Transient & Asymptomatic
      - Clinically Insignificant
    - **Type-II:**
      - Occurs around Day 5 of Treatment
      - Consequence of an Immune Reaction
      - Associated with a Thrombo-embolic Risk.
  - **Theory behind *Heparin-Induced Thrombocytopaenia*:**
    - *Antibodies* (IgG & IgM) directed against Complexes of *Heparin* & *Platelet-Factor-4*.
    - Binding of Antibodies to Heparin:PF4 forms an Immune Complex (Ab:Hep:PF4) which *Activates Platelets* → Thrombus Formation (→Thrombocytopaenia).

- **(Low Molecular-Weight Heparins (LMWH)):**
  - **What are they?:**
    - = Small Heparin Fragments
  - **Mechanism of Action:**
    - Binds & Activates ***Antithrombin-III*** to form an ***AT-III:Heparin Complex***. (Same as Heparin)
      - #1. → **Inactivates Factor-X:**
        - Therefore Inhibits activation of Fibrinogen to Fibrin.
    - **NB: *However,* LMWHs are *Too Small* to inactivate Thrombin :. Only target Factor-X.**
  - **Advantages over *Normal* Heparin:**
    - Longer $T_{1/2}$
    - Self-Administration (Sub-Cut Injection)
    - Dose-Effects are more predictable
    - NO need for monitoring (Ie. Pt can go home → Frees up a hospital bed)
    - (However, it is quite expensive)

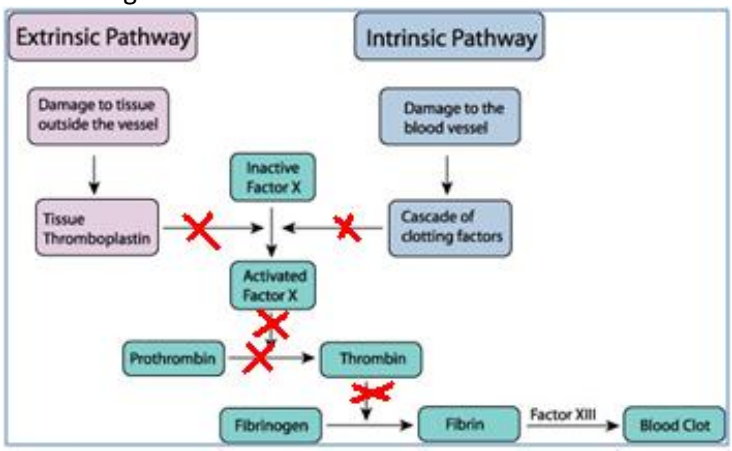






- **Coumarins/Coumadins (Warfarin):**
  - **Mechanism of Action:**
    - A **Vitamin-K Analogue** → Inhibits synthesis of Pro-Coagulation Factors:
      - ↓***Prothrombin***
      - ↓***Factor-II* (Thrombin)**
      - ↓***Factor-VII***
      - ↓***Factor-IX***
      - ↓***Factor-X***

      } Ie. **All TV Channels**
    - **Explanation:**
      - ***Normally*: Vit.K is activated by *'Epoxide Reductase'***, allowing it to aid in the synthesis of the above coagulation factors.
      - ***Warfarin*: Warfarin *Competes* with Vit.K for *'Epoxide Reductase'***, reducing synthesis of coagulation factors.

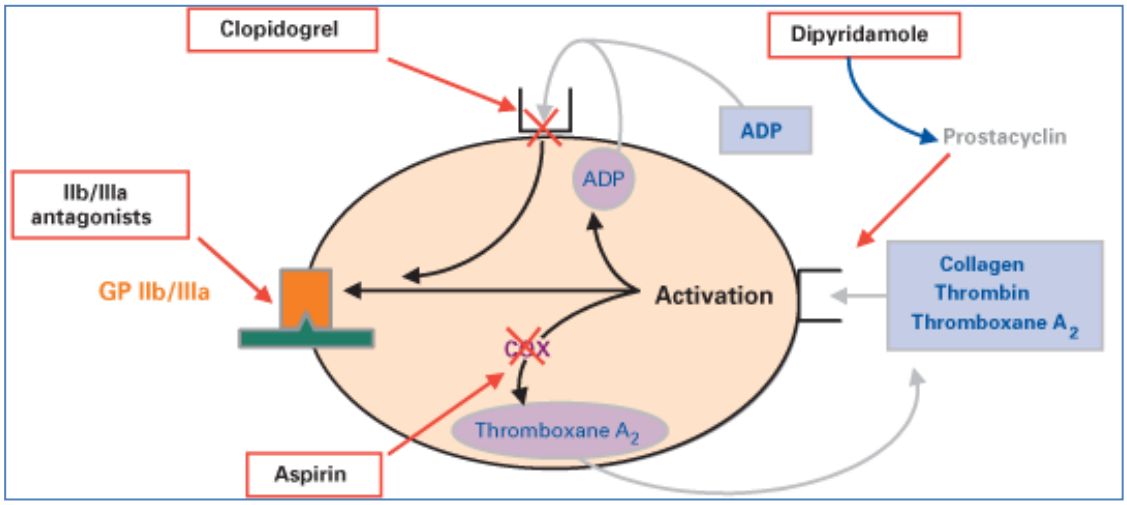


  - **Indications:**
    - Prophylaxis against inappropriate thrombosis/embolism in Predisposed individuals:
      - Eg. Atrial Fibrillation
      - Eg. Artificial Heart Valves
      - Eg. Deep Vein Thrombosis (DVT)
      - Eg. Pulmonary Embolism
  - **Side Effects:**
    - *Bleeding – (However ***Vitamin-K*** is an antidote)
    - NB: Many factors influence effectiveness:
      - (Diet/Alcohol/Body Mass/Other Meds/Alternative Meds/Comorbidity/genetics)
    - Is TERATOGENIC – *CONTRAindicated* in Pregnancy.
  - **Drug Interactions:**
    - Warfarin is metabolised by Cytochrome-P-450 Liver Enzymes.
    - Therefore, *any drug* that Induces CYP-450 enzymes significantly reduces effect of Warfarin.
      - ***Eg. Carbamazepine, Phenytoin, Phenobarbitone – ANTI-EPILEPTICS!!!***
  - **Other Info:**
    - **Slow Onset –** (Takes several days for sufficient competition to occur & for pre-existing coagulation factors to be used up)
    - Used for *Long-Term* home-management & doesn't require monitoring.
    - NB: Vitamin.K can be used as an *Antidote* for Warfarin Overdose.
      - Similarly, a high Vit.K diet can decrease warfarin's effectiveness.

  - **GLS Question: Why MUST you monitor the Prothrombin (PT) Time of Pts on Warfarin?:**
    - (NB: PT = Time taken for plasma to clot after addition of *Tissue Factor* –AKA. Thromboplastin. - It is a Measure of the main *Extrinsic Pathway* coagulation factor – Factor VII)
    - **So Why is PT Monitored with Warfarin?**
      - Need a fine balance between Too Little (→ Coagulation), and Too Much (→Bleeding)
      - *Also*, Warfarin Therapy is complicated because:
        - a) The *Effect* of each dose is ≈2days *After* Administration.
        - b) Numerous Medical/Environmental conditions alter warfarin effectiveness.

ANTI-PLATELET DRUGS:

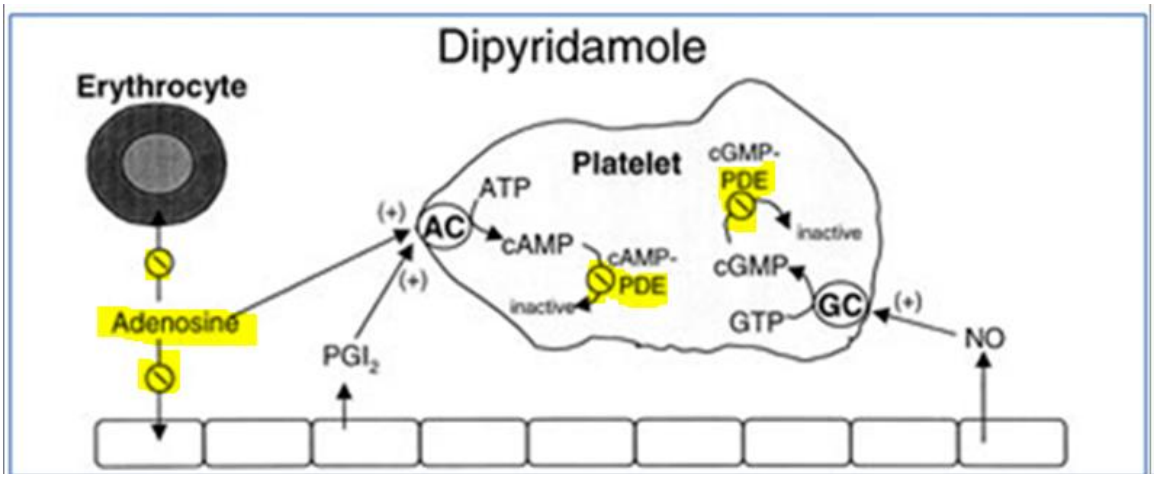
- ****Aspirin:**
  - **Mechanism of Action:**
    - **COX-I Inhibitor – *Irreversibly* Inhibits Cyclo-Oxygenase-1** (COX-1)→ Prevents **Thromboxane** formation from Arachidonic Acid.
      - (COX-1 (and COX-2) is responsible for Prostanoid synthesis [ie. Prostaglandins, Thromboxane & Prostacyclin] from Arachidonic Acid, and is expressed by all cells)
        - (Cox-2 is only expressed during inflammation & wound healing)
      - (NB: Thromboxane is a Platelet-Aggregator – Acts by stimulating the expression of the Glycoprotein receptor "GP-IIb/IIIa" → Aggregation)
    - **NB:** Aspirin blocks a Platelet's Thromboxane-forming abilities for the life of the platelet.
      - **Why? –** Because platelets have NO Nucleus → Can't Re-synthesize Cyclo-oxygenase.
      - **Therefore –** Aspirin has an '*apparent*' selectivity for Platelets.



(NB: Action for Dipyridamole is WRONG in this diagram)

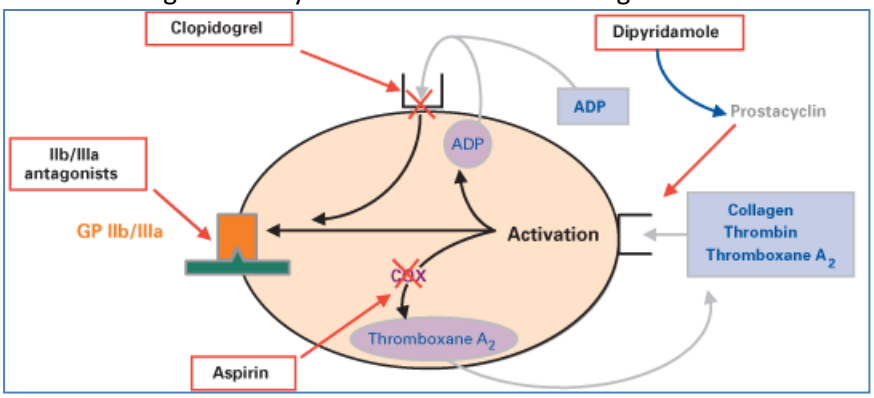
  - **Indications:**
    - Reduce risk of Myocardial Infarction/Angina
    - Acute Stroke
  - **Side Effects:**
    - GI-Bleeding (due to loss of Prostaglandins [which are protective by ↓Acid & ↑Mucus])
    - Toxic dose can cause Respiratory Alkalosis
  - **Other Info:**
    - NB: Antiplatelet effects of Aspirin occur at *Low Doses*. (≈100-300mg/day)
      - Headaches ≈ 600-900mg/day
      - Anti-Inflammatory ≈ 5000mg/day (BUT → Now Obsolete due to GI Problems)

- **Dipyridamole:**
  - **2x Mechanisms of Action:**
    - **Phosphodiesterase (PDE) Inhibitor:**
      - (NB: PDE normally inactivates cAMP)
      - PDE-Inhibitors *Prevent* inactivation of cAMP (& cGMP)→ **↑cAMP →**
    - **Adenosine Uptake Blocker:**
      - → Increased Intracellular Adenosine (the major constituent of cAMP)→ **↑cAMP →**
      - (Adenosine also acts as a Vasodilator)
      - **→↑cAMP→**↑cAMP Inhibits Platelet Aggregation by **decreasing Cytosolic Ca^+ Levels**.
        - ↓Ca^+ **→ Inhibits Ca-Mediated Vesicular Exocytosis of Pro-Aggregation Factors** from the Platelet (Particularly Thromboxane).



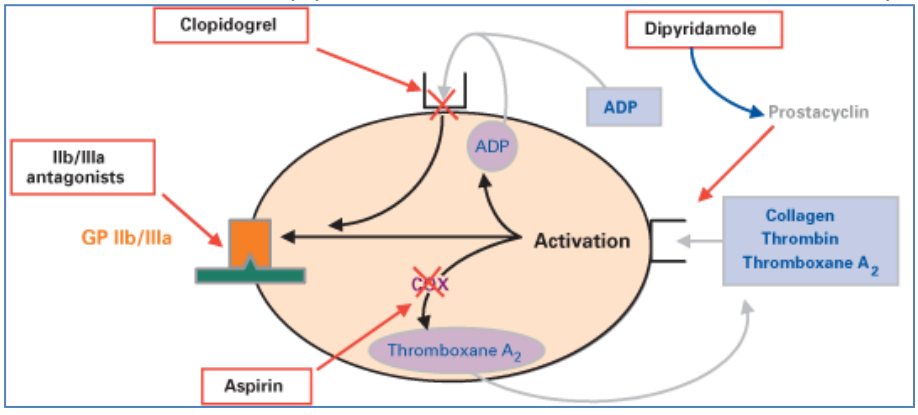
  - **Indications:**
    - Secondary Prevention of Ischaemic Stroke
    - Secondary Prevention of Transient Ischaemic Attacks (TIAs – 'Mini strokes')
  - **Side Effects:**
    - Headache
    - GIT Disturbances
    - Hypotension
    - Allergy

- **Clopidogrel:**
  - **Mechanism of Action:**
    - **ADP-Receptor Antagonists** → Prevents Binding of ADP to platelet→
      - → Prevents ADP-Mediated activation of Glycoprotein Receptor "GP-IIb/IIIa" →
        - → Prevents Platelet-Aggregation
  - **Indications:**
    - (Originally used for Patients Intolerant to Aspirin – now *also* used in conjunction with Aspirin)
    - Myocardial Infarction (Prevention & Treatment)
  - **Side Effects:**
    - Bleeding
    - GI Discomfort
    - Rashes
  - **Other Info:**
    - Is a 'Pro-Drug' → Must be metabolised by Cytochrome-P450 enzymes to be Activated.
      - (NB: Active metabolite is unknown)
    - Onset Takes ≈ 8-10 days.
    - Action is augmented by other Antithrombotic Drugs.



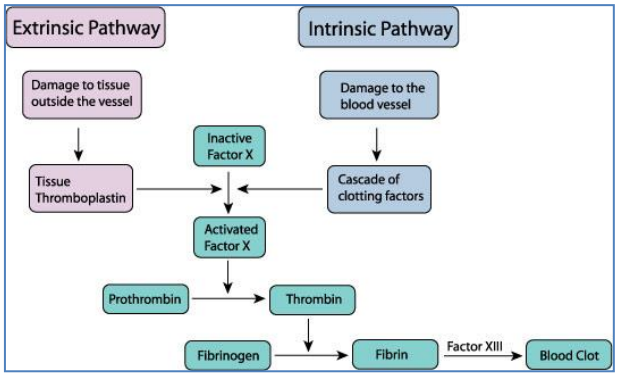
(NB: Action for Dipyridamole is WRONG in this diagram)

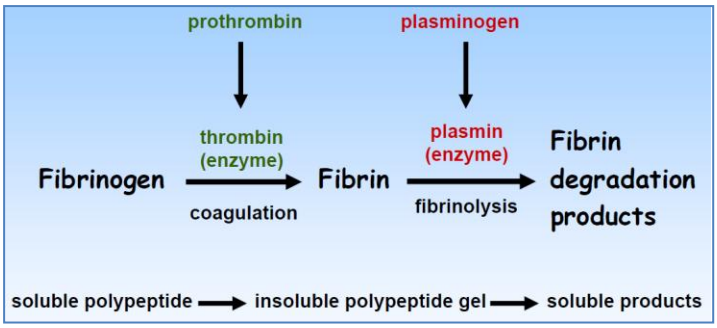
- **ABCIXIMAB (Yes, that is its *actual* name):**
  - **Mechanism of Action:**
    - **GP-IIb/IIIa Antagonist:**
    - A Monoclonal Antibody against the Platelet Glycoprotein Receptor "GP-IIb/IIIa"
      - (GP-IIb/IIIa Destruction → No Aggregation)
    - Surface-Proteins:
      - Vitronectin Receptors (which play a major role in platelet aggregation)
  - **Indications:**
    - Used in Angioplasty (ie. Widening a narrowed/obstructed vessel – Typically Atherosclerotic)
    - Possible use in preventing Thrombus/Embolus complications during Neurovascular Surgery.
  - **Side Effects:**
    - Bleeding
    - Thrombocytopaenia
  - **Other Information:**
    - NB: The name is simply the 'well number' + MAB (monoclonal antibody)



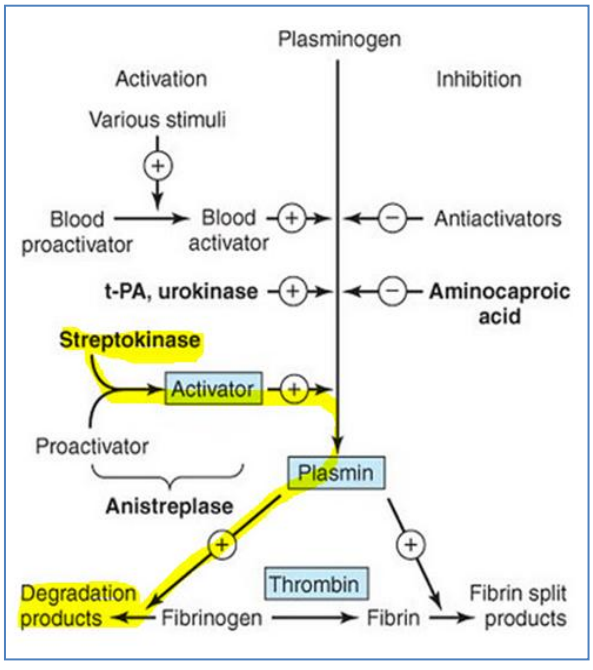
THROMBOLYTICS:

- **NB: Schematic of Fibrin Formation & Degredation:**



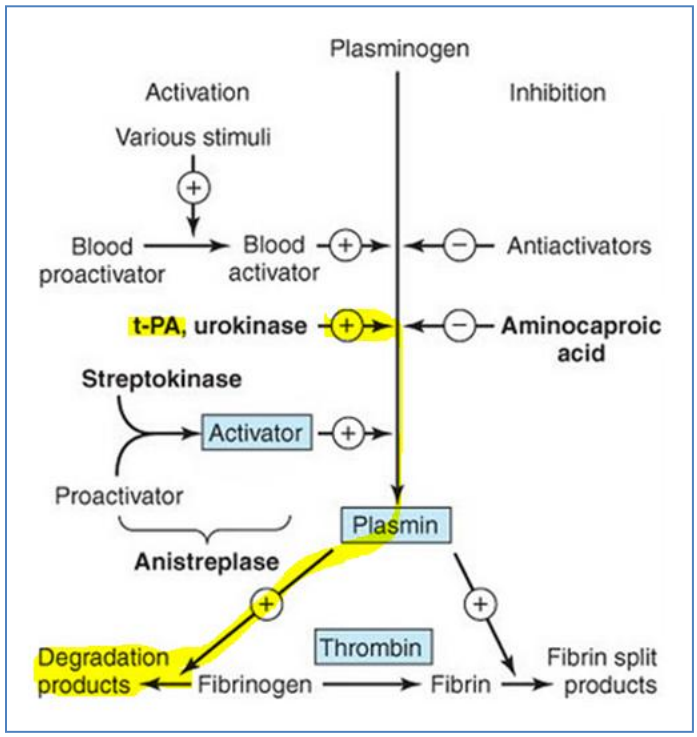


- **Streptokinase:**
  - **Mechanism of Action:**
    - An exogenous Plasminogen Activator (Catalyses conversion of Plasminogen to Plasmin).
      - → Plasmin Degrades Fibrin
  - **Indications:**
    - Thrombolysis of Inappropriate Blood Clots:
      - Pulmonary Embolism
      - Myocardial Infarction
      - Stroke
  - **Side Effects:**
    - Risk of Haemorrhage
  - **Other Info:**
    - Derived from *Haemolytic*-Streptococci Bacteria.
    - *Inhibited by Lipoprotein$_a$ (an endogenous lipoprotein now considered a risk factor for MI)



  - **GLS Question – Why is Streptokinase used *less often* in North Queensland & NT than Vic/NSW?**
    - There is a Higher incidence of Streptococcal infections in tropical Australia than down south.
    - **Why is this a problem?**
      - Previous Strep exposure, & therefore the presence of *Anti-Strep-Antibodies* are a problem for 2 Reasons:
        - a) The Antibodies *destroy* the Streptokinase → rendering it ineffective.
        - b) The Immune *Response* to the Streptokinase can → Hypersensitivity.

- ***(Exogenous) Recombinant* Tissue Plasminogen Activator (r-tPA):**
  - **NB: Tissue Plasminogen Activator (tPA) is normally a protein expressed on Endothelial Cells lining *Undamaged* Blood Vessels:**
    - Its role is to prevent inappropriate fibrin-clot formation in *Intact* Vessels.
    - ***However,* tPA can be Manufactured using *Recombinant Biotechnology* → r-tPA:**
      - **Ie. "*Alteplase*/*Tenecteplase*/*Reteplase*".**
  - **Mechanism of Action:**
    - Exogenous Plasminogen Activator (Catalyse conversion of Plasminogen to Plasmin).
      - → Plasmin Degrades Fibrin → Thrombolysis
  - **Indications:**
    - Thrombolysis of Inappropriate Blood Clots:
      - Pulmonary Embolism
      - Myocardial Infarction
      - Deep Vein Thrombosis
      - Stroke
    - Novel use = *Frostbite* → fewer amputations.
  - **Side Effects:**
    - Risk of Haemorrhage (However, is 'clot-specific' → fewer haemorrhages)
      - (However, in tPA Overdose, ***Aminocaproic Acid*** is an Antidote.)
    - Nausea/Vomiting
    - *Inhibited by Lipoprotein$_a$ (an endogenous lipoprotein now considered a risk factor for MI)
  - **Other Info:**
    - Very expensive (Sometimes Not Cost-Effective)

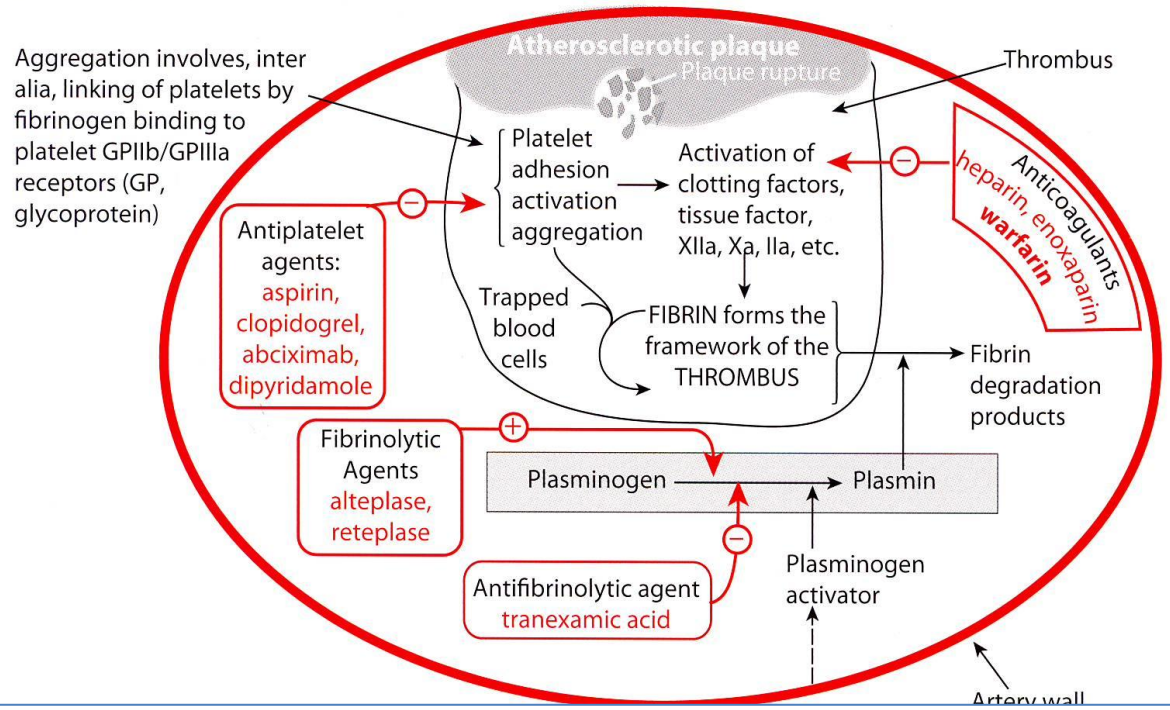


SUMMARY OF HAEMOSTASIS DRUGS & SITES OF ACTION:

10.10 Thrombosis

Anticoagulants are used mainly for thromboembolism in ... ? ... vessels because ... ... ?
Antiplatelet drugs are used mainly for thromboembolism in ... ? ... because ... ... ?

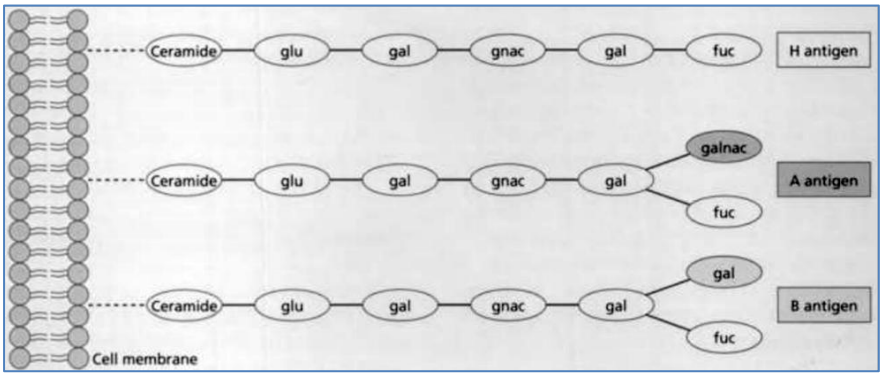
The basic processes involved in the formation of a thrombus and its dissolution by fibrinolysis



Blood Groups: Transfusion & Blood Products.

Blood Types:

- **Blood Group Antigens:**
  - There are ≈400 known RBC Antigens.
  - We are only concerned with 2 of these; the ABO & Rh Antigens.
  - **'ABO' Blood Group Antigens:**
    - Sugar Chains emanating from the RBC membrane
      - A-Antigen
      - B-Antigen
      - A & B-Antigens
      - H-Antigen (O-Type)
        - Such antigens are present on most body cells (incl. White cells & Platelets)



    - Determines the 'A/B/AB/O' blood types.
    - Exist due to 3 allelic genes (A, B & O)
      - A & B alleles can show *CoDominance* (AB-Type)
      - A & B alleles are Dominant over the 'O' allele.
      - Homozygous 'OO' is dominant over A or B alleles.

Mendelian Combinations:

ABO BLOOD GROUP SYSTEMS

Genotype	Phenotype	RBC Ag	Naturally occurring Ab	
OO	O	O	Anti-A & Anti-B	- Can donate to anyone, but can only receive O.
AA or AO	A	A	Anti-B	
BB or BO	B	B	Anti-A	
AB	AB	AB	Nil	Can receive any blood type. - But can only donate to AB

  - **'Rh' Blood Group Antigens:**
    - Membrane-Bound protein on RBC.
    - Presence/Absence of the Rh'D'-Gene determines +ve/-ve blood type.
      - Presence of RhD → Positive
      - Absence of RhD → Negative

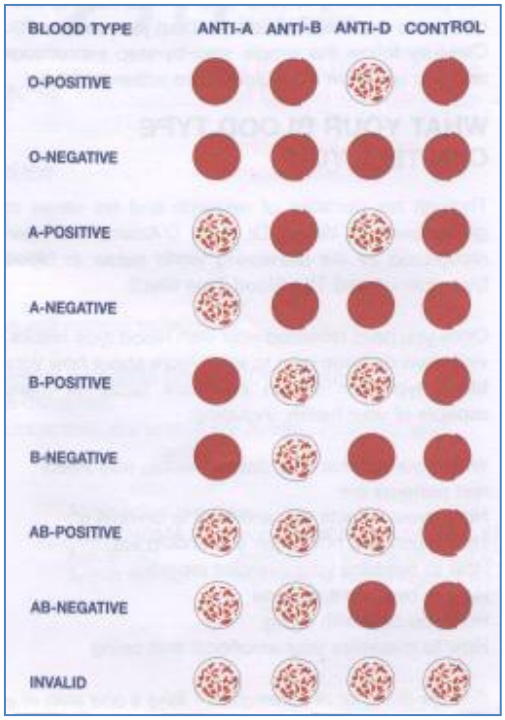
Rh BLOOD GROUP SYSTEMS

CDE system	Short symbol	Rh D status	
cde/cde	rr	Negative	
CDe/cde	R_1r	Positive	
CDe/CDe	R_1R_1	Positive	95% of people are Rh Positive
cDE/cde	R_2r	Positive	
CDe/cDE	R_1R_2	Positive	
cDE/cDE	R_2R_2	Positive	
Others		Positive	

Rh antigens are made up of 3 genes:
- C, D & E

- **Blood Group Antibodies:**
  - **Anti-A / Anti-B:**
  - **Naturally-Occurring Antibodies:**
    - Naturally-Occurring – ie. Born with.
    - Are Immunoglobulins of *type: 'IgM'*
      - AKA: 'Cold Antibodies' – due to low optimum reaction temp. ($4^{o}C$)
    - In *plasma* of people who lack the corresponding Antigen.
      - Eg. A-type individual will have 'Anti-B' Antibodies (against B-Antigens).
      - Eg. O-type individual will have 'Anti-A' & 'Anti-B' Antibodies.
    - If Antibodies contact their respective Antigen, A Haemolytic Reaction may occur.
  - **Anti-D:**
  - **Immune Antibodies:**
    - Immune – ie. Produced in *response to introduction*
      - Via transfusion ...or
      - Trans-Placental Passage
    - Are Immunoglobulins of *type: 'IgG'*
      - AKA: 'Warm Antibodies' – due to higher optimum reaction temp. ($37^{o}C$)
      - NB: Only IgG-Ab's are capable of trans-placental passage.
    - Most Important IgG = the 'Rh-Antibody' (Anti-D)

'Well' Method of Blood Typing:



Diamed Gel Card Method of Blood Typing:

Agglutination reactions are those suspended in the gel - ie. Due to clumping, the cells cannot fit between the gel particles. (similar to gel electrophoresis)

- **Common Blood Groups & Characteristics:**

Phenotype	Genotype	RBC Antigens	Naturally occurring antibodies	Frequency
O	OO	None	AB	40%
A	AA, AO	A	B	30%
B	BB, BO	B	A	25%
AB	AB	A & B	None	5%
(Rh-D Positive)		D	No anti-D	
(Rh-D Negative)		-	Anti-D	

- **Universal Donor:**
  - O-Negative
    - No A or B Antigens
    - No Rh-D Antigens

- **Universal Recipient:**
  - AB-Positive
    - No anti-A or anti-B Antibodies
    - No anti-Rh-D Antibodies
- **Group Specific Blood Vs. Cross Matched Blood:**
  - **Group Specific =** Blood of any 'Type' (ABO,D) that's compatible with the Recipient. (20mins)
  - **Cross Matched =** Complex Pre-Transfusion Testing for Compatibility across *all* Blood Types. (1hr)

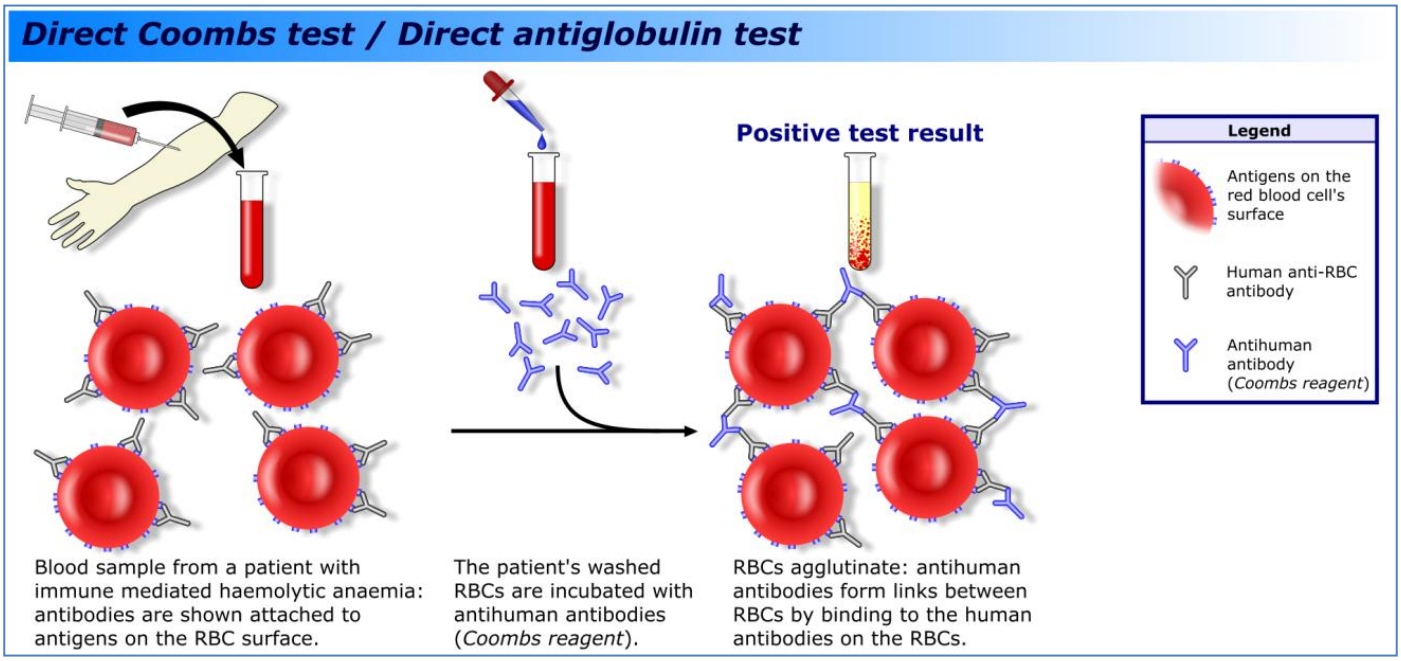
- **In Emergency Situations:**
  - Sometimes there isn't time to obtain a blood group or do a full cross match, so it is best to give O-Neg in an emergency situation.

Blood Donation Process:

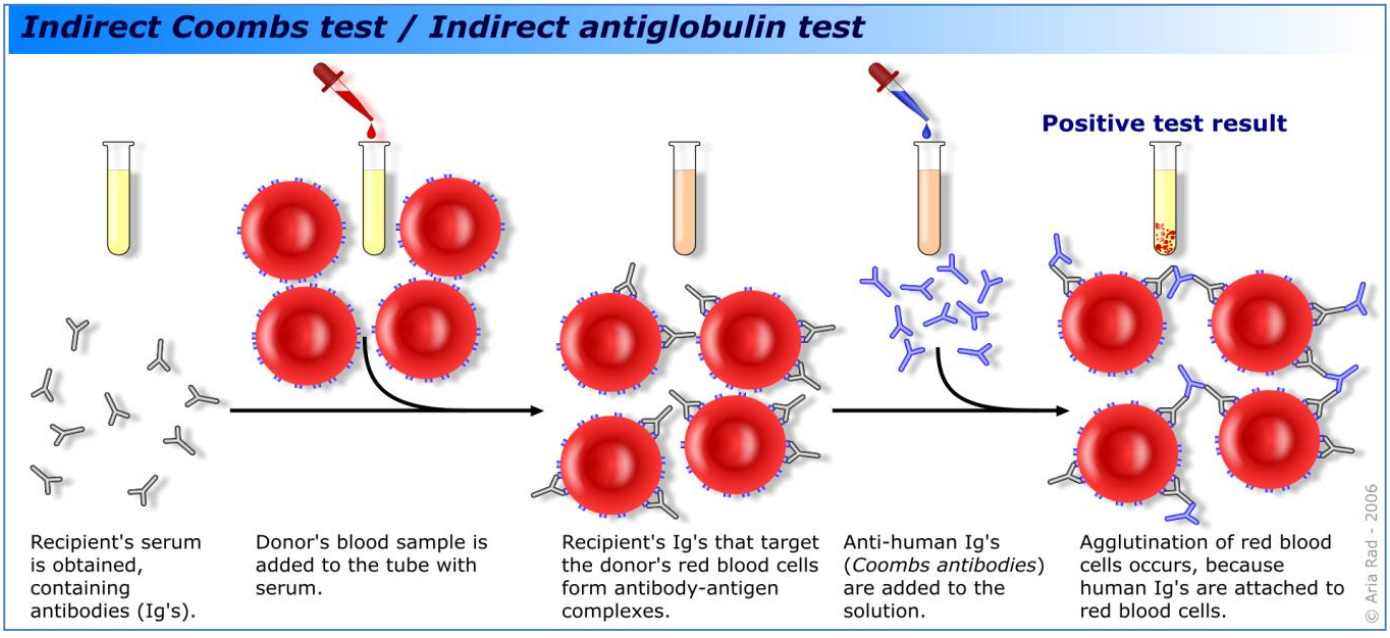
- **1. Blood Donation:**
  - Donors carefully selected:
    - Healthy
    - 18-65yrs
    - Minimum Hb Level (not anaemic)
    - No infection
    - No Meds/Drugs
  - Frequency: 2-3times/year
  - Volume: 450mL (A *Pint*)
- **2. Collection:**
  - Stored in PVC Bag
  - With Anticoagulants:
    - Citric Acid
    - Na
    - Sodium Phosphate (NaH_2PO_4)
  - Additive Solution:
    - Adenine – for ATP production
    - Glucose – to feed Glycolysis
    - Saline – maintain isotonic
  - Bags are refrigerated – NOT FROZEN – Freezing would crystalise cells →lysis.
- **3. Lab Screening:**
  - HIV
  - Hep B/C
  - HTLV (Leukaemia Virus)

- CMV (Cytomegalovirus)
- Syphilis

- **4. Serology Tests:**
  - **ABO Typing:**
    - By Addition of Antibodies 'A' & 'B' to blood sample.
      - If Type-A: Reacts if 'A-Antibodies' added.
      - If Type-B: Reacts if 'B-Antibodies' added.
      - If Type-AB: Reacts if 'A' or 'B-Antibodies' added.
      - If Type-O: No reaction with addition of either 'A'/'B'.
    - Reaction = Agglutination of RBCs. (Not Clotting)
  - **Rh D Typing:**
    - By Addition of Antibody-'D' to blood sample
      - If Positive: Agglutination Reaction
      - If Negative: No Reaction
    - Reaction = Agglutination of RBCs. (Not Clotting)
  - Rh C & E Typing
  - Screening for serum RBC Antibodies
- **5. Quality Assurance Tests:**
  - Whole Blood Volume
  - RBC Concentrate – (Packed Cell Volume)
  - Platelet Concentrate
  - Fresh Frozen Plasma Volume
    - Factor VIII Concentration
  - Sterility Testing
- **6. Pre-Transfusion Tests:**
  - Recipient's Blood is Typed.
  - **Cross-Matching:**
    - Testing Donor-RBC's against *serum* of patient.
    - Ie. Mixing the 2 blood samples (recipient & donor) – check for reaction.
  - To ensure donor-recipient compatibility.
  - Still a slight possibility of mismatch even between 'compatible' patients (due to other RBC Antigens)
- **Antiglobulin Test (Coomb's Test):**
  - 2 Clinical Blood Tests – Direct & Indirect
    - **Direct (DAT):**
      - Detect if antibodies or complement have bound to RBC surface antigens *in vivo.*
      - Used clinically when immune-mediated *hemolytic anemia* (antibody-mediated destruction of RBCs) is suspected.
      - A Positive Result →means an immune mechanism is attacking the patient's RBC's.
- **How long can blood be stored for?**
  - 5-6 weeks

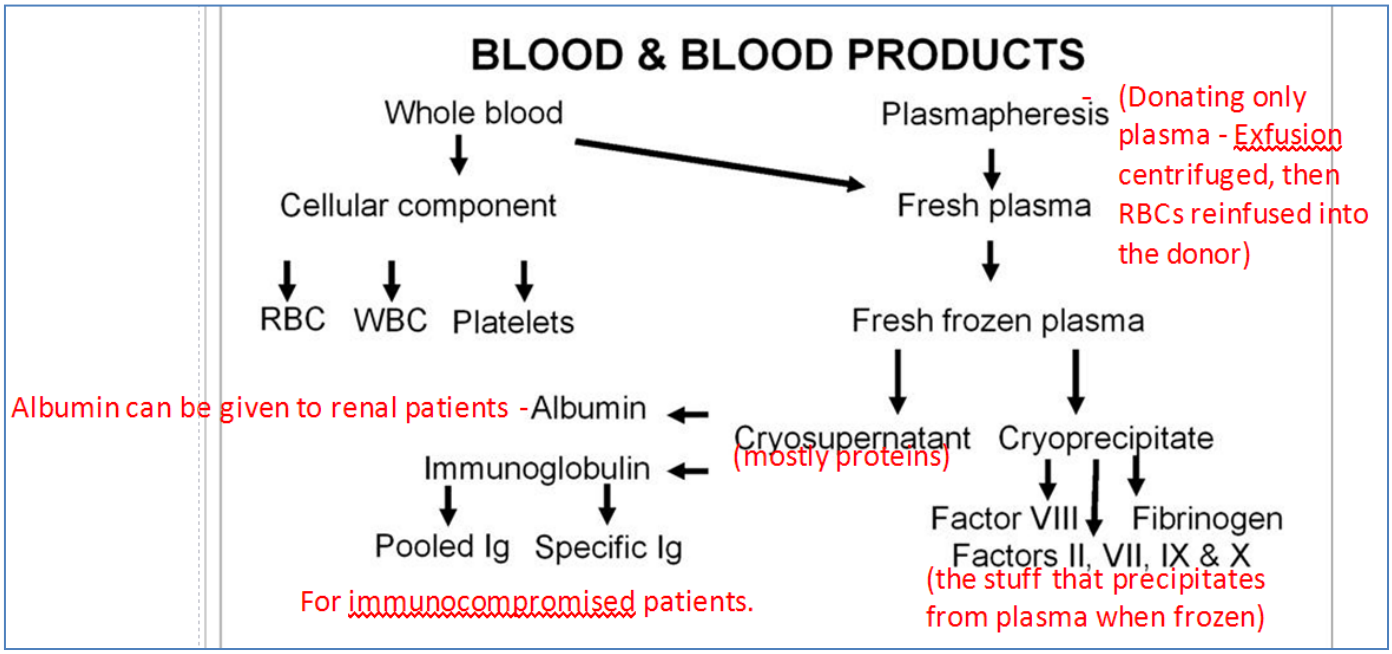


- **Indirect (IDAT):**
  - Detects antibodies against RBCs present in the patient's serum.
  - Serum is extracted from the blood, and is incubated with RBCs of known antigenicity.
  - If agglutination occurs, the indirect Coombs test is positive.
  - It is used to detect very low concentrations of antibodies present in a patient's plasma/serum *prior to a blood transfusion*.
  - *In antenatal care*, the IAT is used to screen pregnant women for antibodies that may cause *haemolytic disease of the newborn.*



Blood Products:

- **--Whole Blood:**
  - Cells/Platelets
  - Plasma
  - **Reason For Transfusion:**
    - Acute Blood Loss
- **Packed Red Blood Cells:**
  - RBC's
  - **Reasons for Transfusion of RBCs:**
    - **Mainly to *Quickly improve O_2 Delivery to Tissues.***
      - Expect a rise of *10g/L* of Haemoglobin *Per Unit of Blood (450mL)*
    - **Egs of Eligable Recipients:**
      - Acute Blood Loss
      - Preoperative
      - Anaemias
      - Renal failure
      - Bone Marrow Failure
      - Septicaemia
      - Haemolytic Disease of the Newborn.
- **Granulocyte Concentrates:**
  - White Blood Cells (leukocytes)
  - **Reason For Transfusion:**
    - Supportive Therapy for Neutropenia (Low White Cell Count)
    - Eg. Pts following radiotherapy.
- **Platelet Concentrate:**
  - Platelets
  - **Reasons For Transfusion:**
    - Severe Thrombocytopenia
    - Severe Bone-Marrow Failure (Ie. Acute Leukaemia)
    - Myelotoxic Chemotherapy
- **--Plasma:**
  - Blood proteins
  - Clotting Factors
  - **Reasons For Transfusion:**
    - Replacement of Coagulation Factors
    - Eg. Haemophilia & other Bleeding Disorders.
- **Cryoprecipitate:**
  - Clotting Factors
  - Fibrinogen
  - **Reasons For Transfusion:**
    - Used To Control Clotting Disorders.
    - **Factor VIII & Fibrinogen:**
      - Treatment of Haemophilia
    - **Factor IX & Prothrombin:**
      - Treatment of Factor IX Deficiency
      - Treatment of Christmas Disease.
- **Cryosupernatant:**
  - Albumin
  - Immunoglobulins
  - **Reasons For Transfusion:**
    - Used as 'Volume Expanders' – in Hypovolumic Shock
    - **Albumin:**
      - Volume Expander
      - To Treat HypoAlbuminaemia – eg. Burns/Renal Patients.
    - **Immunoblobulins:**
      - Treatment of Immunocompromised Patients


BLOOD & BLOOD PRODUCTS
Whole blood
Cellular component
RBC
WBC
Platelets
Plasmapheresis
(Donating only plasma - Exfusion centrifuged, then RBCs reinfused into the donor)
Fresh plasma
Fresh frozen plasma
Albumin can be given to renal patients -Albumin
Cryosupernatant
(mostly proteins)
Cryoprecipitate
Immunoglobulin
Factor VIII
Fibrinogen
Factors II, VII, IX & X
Pooled Ig
Specific Ig
For immunocompromised patients.
(the stuff that precipitates from plasma when frozen)

Blood Transfusion:

- Involves the infusion of blood from a donor to a recipient
- Compatibility between *Donor RBC Antigens* & *Recipient Plasma Antibodies* Essential.
    - If incompatible – haemolytic reaction may occur.

Complications of Blood Transfusion:

- **Immediate:**
    - Directly after transfusion
    - **Immunological:**
        - **Haemolytic Reaction -** Fever, Tachycardia, Hypotension, Shock
            - Reaction → Intravascular Haemolysis
            - Ie. Rapid Destruction of RBCs → Reduced O_2-Carrying Capacity
                - Involving ABO Antibodies = Life threatening
                - Involving Rh Antibodies = Less severe
            - Managed by Maintaining BP & Renal Perfusion (by giving Plasma & Diuretics)
        - **Pyrogenic Reaction –** Fever
            - Due antibodies formed after previous sensitisation (Transfusion/Pregnancy)
        - **Allergic Reactions.**
            - Triggered by IgE Antibodies (covered more in 4^{th} year)
            - May result in Anaphylactic Shock

    - **Non-Immunological:**
        - **Bacterial Contamination**
        - **Circulatory Overload → Left Ventricular Failure**
        - **Hyperkalaemia** – Excess Blood K^+
        - **Clotting Abnormalities**

- **Delayed:**
    - A while after transfusion
    - **Immunological:**
        - **Delayed Haemolytic Reactions**
        - **Alloimunisation** - development of antibodies in response to alloantigens (antigens derived from a genetically dissimilar animal of the same species)
        - **Graft-Versus-Host-Disease** – Where immune cells in the transfused blood recognizes the recipient as "foreign" and mounts an immunologic attack.

    - **Non-Immunological:**
        - **Infectious Disease –** eg. HIV, Hep-B/C, Bacteria, Parasites
        - **Iron Overload** - accumulation of iron in the body – Affects liver, heart & endocrine glands.
            - Occurs in people who rely on Regular RBC Transfusion.
            - Eg. Renal patients – lack erythropoietin.
            - Excessive transfusion → Iron overload.

Artificial Oxygen Carriers as RBC Substitutes:

- Technologies that are being developed to replace red blood cell transfusions.
    - Benefits:
        - Eliminates risk of transfusion complications
        - Overcomes the problem of donor deficiency
- **Haemoglobin-Based Oxygen Carriers:**
    - Direct infusion of Hb molecules
    - However, when Hb is taken out of the RBC, it tends to break apart, and it also loses its oxygen affinity.
    - To overcome this problem, Hb is inserted into liposomes to mimic the red blood cells.
- **Perfluorocarbons (PFCs)**
    - After IV administration, PFCs are taken up by reticuloendothelial cells.
    - Chemically inert molecules with oxygen binding & giving-off ability.
    - However, doesn't have the same oxygen association curve as Hb.

HAEMATOLOGY Pathology:
APLASTIC ANAEMIA

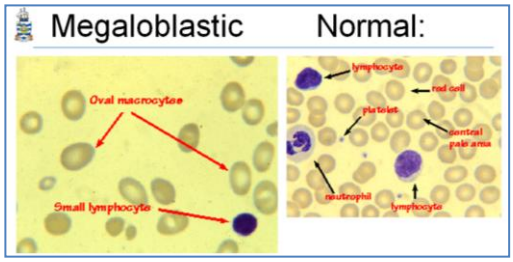
APLASTIC ANAEMIA (Ie. MARROW FAILURE):

- (Aplastic Anaemia = "Pancytopaenia wityh Bone Marrow *Hypo*cellularity (aplasia))
- **Aetiology:**
  - **Simple Bone Marrow Failure (NOT Malignant)**
    - **Primary:**
      - Congenital
      - Idiopathic
    - **Secondary:**
      - Cytotoxic Drugs
      - Sensitivity to other drugs (Eg. Chloramphenicol, Chlorpromazine, Phenytoin, NSAIDs)
      - Ionizing Radiation
- **Pathogenesis:**
  - Reduction in Pluripotent Stem Cells
  - Remaining Stem Cells are *FAULTY* or *IMMUNOGENIC* :. Cannot repopulate the Marrow.
  - → Pancytpopaenia (Deficiency of all cells)
- **Morphology:**
  - Pancytopaenia with Bone Marrow *Hypo*cellularity (Aplasia)
  - There are NO Leukaemic, Cancerous or Abnormal Cells in Marrow OR Peripheral Blood.
- **Clinical Features:**
  - **Symptoms & Signs:**
    - **General Anaemia Symptoms:**
      - Fatigue, Headaches & Faintness
      - Exertional Dyspnoea
      - Exertional Angina
      - Intermittent Claudication
      - (Incl. Exacerbations of CVS/REsp problems in Elderly – Eg. Claudication & Angina)
    - **General Anaemia Signs:**
      - Pallor (Mucosal/Facial/Palmar Crease)
      - Tachycardia
      - Systolic Flow Murmur (Hyperdynamic Circulation)
      - Cardiac Failure
    - **Signs Specific to Aplastic Anaemia:**
      - Anaemia (↓RBCs)
      - Bleeding/Bruising/Petechiae/Bleeding Gums (↓Platelets)
      - Infection (↓WBCs)
  - **Investigations:**
    - ****Bone Marrow Biopsy** – For Hypocellularity – Necessary for Diagnosis
    - **Reticulocyte Count** – Complete *Absence* of Retics.
    - **Blood Count** – Pancytopaenia
  - **Treatment:**
    - ***Bone Marrow Transplant + Supportive Transfusions**

HAEMATOLOGY Pathology:
ANAEMIA - B12 FOLATE DEFICIENCY

MACROCYTIC (MEGALOBLASTIC) ANAEMIA – VitB12/Folate Deficiency:

- **(Including PERNICIOUS ANAEMIA)**
- (2nd most common type of anaemia)
- ("Megaloblasts" = *large, Erythroblasts with Immature Nuclei* - seen in the Marrow)
- **Aetiology:**
  - **Vitamin B12/Folic Acid Deficiency (Deficiency of either →Megaloblastic Anaemia)**
    - ****Malnutrition**
    - ****Alcoholism (or Liver Disease)**
    - ****Pernicious Anaemia** – (↓Parietal Cells → ↓Intrinsic Factor → B12 Malabsorption)
    - **Intrinsic Factor Deficiency**
    - **Cytotoxic Chemo Drugs**
    - **Malabsorption Syndrome – (**Coeliac, IBD, Gastrectomy, Ileal Resection)
    - **Old Age**
- **Pathogenesis:**
  - **VitB12/Folate are Necessary for Nuclear DNA Synthesis :. Bottlenecks RBC Production**
- **Morphology:**
  - **Marrow Biopsy:**
    - **Megaloblasts in Bone Marrow** *(large, Erythroblasts with Immature Nuclei)*
  - **Blood Film:**
    - ***Normochromic**
    - ***Oval Macrocytes (Large, Oval RBCs)**
    - ***Hypersegmented Neutrophils (**Some with >6 Lobes in Nucleus)
    - ***Pancytopenia** (Reduction in Number or ALL Cells – RBCs/WBCs/Platelets)
    - **Attempted ↑↑Erythropoiesis:**
      - **↑Reticulocytes**
      - **Some "Polychromatophils"** (Biger, Blueish RBCs)
      - **Some Nucleated RBCs**
    - **+ An-Isocytosis** (variations in size)
    - **+ Poikilocytosis** (Variations in shape)



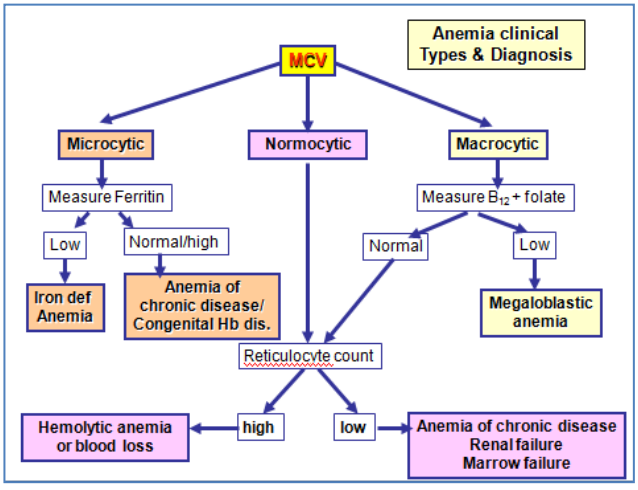
- **Clinical Features:**
  - **General Anaemia Symptoms & Signs:**
  - **Signs & Symptoms Specific to Megaloblastic Anaemia:**
    - Glossitis (Red Sore Tongue)
    - Angular Stomatitis/Cheilitis
    - Peripheral Neuropathy (Paresthesia, ↓Vibration, ↓Proprioception, Weakness & Ataxia)
- **Investigations:**
  - **Blood Film** (Oval Macrocytes, Hypersegmented Neutrophils, Pancytopenia)
  - **FBC** (↑MCV, Pancytopenia)
  - **Bone Marrow Biopsy** (Shows Megaloblasts) – Rarely Required
  - **Serum B12/Folate** (↓ if B12/Folate Deficiency)
- **Treatment:**
  - **Oral B12**
  - **Oral Folate**
  - **Corticosteroids + B12 Supplements (If Pernicious Anaemia)**

HAEMATOLOGY Pathology:
ANAEMIA

ANAEMIAS IN GENERAL

Anaemias:

- **General:**
  - **Definition = "Decreased haemoglobin concentration in blood"**
    - May be Low Hb
    - OR low Hematocrit/Packed Cell Volume.
  - **Normal Hb Range:**
    - 13 - 16g/dl (male) (130-160g/L)
    - 11.5 - 16g/dl (Female) (115-160g/L)
- **Aetiologies:**
  - **Decreased Production** (Fe/Folate/B12 Deficiency incl.Pernicious/Chronic Disease/Aplastic)
  - **Blood Loss** (Haemorrhage/Hookworm/Menorrhagia)
  - **Destruction/Abnormality of RBCs** (Eg. Warm & Cold Haemolytic/Microangiopathy/G6PD/Sickle/Thalassaemia/ Sphreocytosis)
  - **Spurious** (Increased Plasma Volume – Eg. Pregnancy/Fluid Overload)
- **Morphologies:**
  - **Classified by MCV (Mean Cell Volume) & Colour:**
    - Microcytic Hypochromic, Low MCV
    - Macrocytic, High MCV
    - Normocytic, Normochromic, Normal MCV.
  - **Microscopy (Blood Films):**
    - **Iron Deficiency Anaemia:**
      - Hypochromic RBCs - Increased Central Pallor
      - Microcytic
      - Pencil Cells (RBCs with a single sharp edge)
    - **Megaloblastic Anaemia:**
      - Oval Macrocytic RBCs
      - Normochromic
    - **Warm Antibody (IgG) Autoimmune Haemolytic Anaemia:**
      - Microspherocytes (Small, RBCs with No Central Pallor)
      - Evidence of Haemolysis (Reticulocytes, Nucleated RBCs, Schistocytes)
    - **Cold Antibody (IgM) Autoimmune Haemolytic Anaemia:**
      - Agglutination of RBCs (Ugly clumping of) @ <20^{o}C
      - May agglutinate in peripheries @ cold temperatures →Raynaud's Phenomenon
    - **Oxidative Haemolysis (Eg. G6P Deficiency):**
      - (Affects cell fluidity, Hb Condenses)
      - Bite Cells (RBCs) – Macrophages take bites out of RBCs
        - NB: an Indication for Splenectomy.
      - Blister Cells (RBCs)
      - Irregularly contracted microspherocytes



- **Clinical Features:**
  - May be Asymptomatic
  - **General Anaemia Symptoms:**
    - Fatigue, Headaches & Faintness
    - Exertional Dyspnoea
    - Exertional Angina
    - Intermittent Claudication
  - **General Anaemia Signs:**
    - Pallor (Mucosal/Facial/Palmar Crease)
    - Tachycardia
    - Systolic Flow Murmur (Hyperdynamic Circulation)
    - Cardiac Failure
  - **Some Signs Specific to Different *Types* of Anaemia:**
    - Koilonychia (Spoon-shaped nails) – Iron Deficiency
    - Glossitis – Iron/B12 Deficiency
    - Jaundice – Haemolytic Anaemia
    - Splenomegaly – Haemolytic Anaemia, Leukaemia, Lymphoma
    - Bone Pain/Deformities – Thalassemia Major, Myeloma
    - Leg Ulcers – Sickle Cell
- **Investigations:**
  - **Measuring Blood – Blood Count – CBC/FBC:**
    - **Mean Hb Concentration:**
      - Amount of Hb per RBC (g/dL)
    - **Mean Cell Hb:**
      - Weight of Hb per RBC
    - **Mean Cell Volume:**
      - Volume per RBC

Table 2. Differential Diagnosis of Anemia Based on MCV

Hypochromic microcytic (MCV<80)	Normochromic normocytic (80<MCV<100)		Macrocytic (MCV>100)

• Fe deficiency
• Thalassemia
• Lead Poisoning
• Sideroblastic
• Chronic disease (some cases)
	Low Reticultocytes:
	• Myelodysplasia
	• Infiltration (leukemia, myeloma, mets, infection)
	• Myelofibrosis
	• Aplasia
	• Chronic Disease (some cases)
	• Liver Disease
	• Uremia
	• Endocrine (hyper/hypothyroid, Addison's)
		High Reticulocytes:
		• Hemolytic anemia
		• Post-hemorrhagic anemia
		• Treated nutritional deficiency
			• Megaloblastic
			  • B12
			  • Folate
			  • Drugs
			• Myelodysplasia
			• Liver Disease
			• Alcohol
			• Reticulocytosis

  - **Iron Studies:**

Table 4. Interpreting Iron Indices

	Ferritin	Serum Iron	TIBC	RDW	Saturation
Iron Deficiency	↓↓	↓	↑	↑	↓↓
Chronic Disease	↑/N	↓/N	↓/N	N	N
Sideroblastic Anemia	↑	↑	N	No (dimophic picture)	—
Iron Overload	↑	↑	N	—	↑

Differential Diagnosis of Anaemia – Based on Microscopic Features (Mean Cell Volume & Reticulocytes):		
Microscopic Features:	**Differential Diagnoses:**	**Further Lab Evaluation:**
Anaemia **Low MCV (Microcytic)** **Low Retics**	Iron Deficiency Anaemia of Chronic Disease Thalassemia Lead Poisoning	Iron Studies, Fe-Binding, Ferritin Blood Film (Pencil Cells = IDA)
Anaemia **High MCV** **(Macrocyt/Megalo)**	Megaloblastic Anaemia (B12/Folate) Alcohol Abuse Liver Disease Myelodysplastic Syndromes or Leukaemia High Retics? = Bleeding, Haemolysis.	Serum B12 RBC Folate Levels Blood Film (Macroovalcytes, Pancytopenia) Marrow Biopsy (Dysplasia/Neoplasia)
Anaemia **Normal MCV**	Primary Bone Marrow Failure - Aplastic Anaemia/Drugs/Chemo - Leukaemia - Myelodysplastic Syndromes Secondary Bone Marrow Failure - Uraemia - Endocrine Disorder - HIV/AIDS - Anaemia of Chronic Disease Haemoglobinopathies (Sickle/Thalassemia) Haemolysis – Immune/Mech/Toxic.	Blood Smear Iron Studies, Fe-Binding, Ferritin Kidney, Thyroid, Liver Function Tests Cortisol Levels EPO Levels
Anaemia **High Reticulocyte Count**	Bleeding – Blood Loss (Internal/External) Haemolysis – Immune/Mech/Toxic.	Blood Film – nRBC, spherocytes, parasites Bilirubin/Haptoglobin (Haemolysis) Coombe's (Direct & Indirect) G6PD screen.

HAEMATOLOGY Pathology:
ANAEMIA – HAEMOLYTICS

"HA" - HAEMOLYTIC ANAEMIA:

- (Anaemia due to Increased Premature RBC Destruction, and *INADEQUATE* compensation by Bone Marrow)
  - **Intravascular Haemolysis:** Occurs within the ***Circulation***.
  - **Extravascular Haemolysis:** Occurs in the ***Reticuloendothelial System*** (Liver/Spleen/Marrow)
- **Pathogenesis:**
  - **Background of Hb Breakdown:**
    - **Heme Molecule → *Protoporphyrin*** *& Iron*
    - **Protoporphyrin → Bilirubin → Conjugated in Liver** → Excreted in Bile & Faeces.
  - **Pathogenesis of Haemolytic Anaemia):**
    - **Jaundice:** RBC Breakdown → ↑Protoporphyrin →↑Bilirubin (Unconjugated) → Jaundice
    - **Reticulocytosis:** Anaemia → ↑RBC Production → ↑Reticulocytes
    - **Low Haptoglobins:** Depleted Haptoglobins (Hb Carrier Proteins made by the Liver)
- **A 4Q Approach to Haemolytic Anaemias:**
  - **1. Is there ↑ RBC Breakdown?** (Anaemia?/Jaundice?/Urinary Urobilinogen?)
  - **2. Is there ↑ RBC Production?** (Reticulocytes?/↑MCV?/Polychromasia?)
  - **3. *Extravascular* or *Intravascular*?**
    - ***Extravascular =*** (Splenomegaly?)
    - ***Intravascular =*** (↑Plasma Hb?/↓Plasma Haptolobin?/Haemoglobinuria?)
  - **4. Why is there Haemolysis?**
    - **Is it Autoimmune (WAHA/CAHA)? → +ve *Coomb's Tests***
    - **Is it Congenital (Sickle / Thalaaemia / G6PD / Her.Sperocytosis)? → *Blood Smear***
    - **Is it Mechanical (Microangiopathy / March Syndrome / DIC) → *Blood Smear***

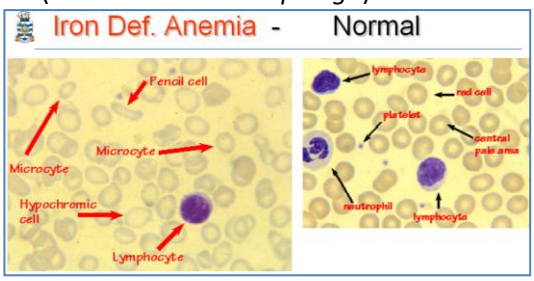
- **Clinical Features:**
  - **Symptoms:**
    - **General Anaemic Symptoms & Signs +**
    - **Specific to Haemolytic Anaemia:**
      - Jaundice (Mild & Fluctuating)
      - Splenomegaly
      - Pigment Gall Stones (If Chronic HA)
      - Venous Stasis Ankle Ulcers (Sickle Cell)
      - Microangiopathy/Infarction/Raynauds
  - **Laboratory Evaluation:**
    - **LFTs – (**↑Bilirubin, ↓ Haptoglobins**)**
    - **Blood Smear – (**Broken RBCs, Congenital RBC Disorders, Anaemia)
    - **Coombe's Test – (**?Autoimmune Haemolytic Anaemia**)**

- **Treatment:**
  - **Treat Underlying Cause**
  - **Plasmapheresis if Autoimmune**
  - **Splenectomy if Hypersplenism/Heriditary Spherocytosis**
  - **Blood Transfusion if Severe**

HAEMATOLOGY Pathology:
IRON DEFICIENCY

"IDA" - IRON DEFICIENCY ANAEMIA (Microcytic):

- (Most common type of Anaemia)
- **Aetiology:**
  - **Chronic blood loss → MOST common cause of Iron Deficiency**
    - (Eg. Parasitic Worm Infestation, Malignancy, Menorrhagia, GI Ulcers)
  - **Increased Need (Over-Demand):**
    - Pregnancy, Rapid Growth (children)
  - **Poor diet / poor absorption:**
    - Malnutrition (↓Greens & Meat)
    - Malabsorption, intestinal surgery, gastric atrophy.
- **Pathogenesis:**
  - Iron is a fundamental constituent of Haemoglobin :. ↓Fe →↓Hb Synthesis →Anaemia.
- **Morphology – Blood Film:**
  - **Microcytic (↑Divisions of Progenitors)** (↓MCV)
  - **Hypochromic (↑Central Pallor of RBCs)** (↓Hb Content)
  - **+ An-Isocytosis** (variations in size)
  - **+ Poikilocytosis** (Variations in shape)
  - **+ Some "Pencil Cells".** (RBCs with one *Sharp Edge*)

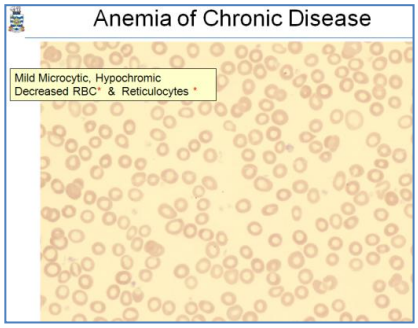


- **Clinical Features:**
  - **Symptoms & Signs:**
    - **General Anaemia Symptoms:**
      - Fatigue, Headaches & Faintness
      - Exertional Dyspnoea
      - Exertional Angina
      - Intermittent Claudication
      - (Incl. Exacerbations of CVS/REsp problems in Elderly – Eg. Claudication & Angina)
    - **General Anaemia Signs:**
      - Pallor (Mucosal/Facial/Palmar Crease)
      - Tachycardia
      - Systolic Flow Murmur (Hyperdynamic Circulation)
      - Cardiac Failure (Eg. Pedal Oedema)
    - **Signs Specific to Iron Deficiency Anaemia:**
      - (All due to cytochrome oxidase functional deficiency – Which requires iron to work)
        - *****Atrophic Glossitis (Atrophy of Papillae of tongue)***
        - ****Angular Cheilitis/Stomatitis***
        - ****Koilonychia (Spoon Nails)***
        - **** Brittle Nails, Brittle Hair***
  - **Diagnosis:**
    - **Blood Count & Film** (Microcytic, Hypochromic, Poikilocytosis, Anisocytosis, Pencils)
    - **Iron Studies** (↓Ferritin;↓Iron; ↑TIBC)
  - **Differentials (for low MCV):**
    - Thalassaemia
    - Anaemia of Chronic Disease
    - Sideroblastic Anaemia (Very Rare)
  - **Treatment:**
    - Iron Supplementation

HAEMATOLOGY Pathology:
ANAEMIA – NORMOCYTICS

ANAEMIA OF CHRONIC *Inflammatory* DISEASE (Microcytic):

- **Aetiology:**
  - **Chronic Infection** (Eg. Tuberculosis)
  - **Chronic Inflammatory Disease** (Eg. Crohn's/Rh.Arthritis/SLE/Malignancy)
- **Pathogenesis:**
  - **Chronic Infection/Inflammation →**
    - ↓RBC Survival
    - ↓EPO Release
    - ↓Iron Transfer ... →Anaemia
- **Morphology:**
  - Typically Normocytic (Sometimes Microcytic) [Debatable]
  - Hypochromic
  - Fewer RBCs



- **Clinical Features:**
  - **Symptoms & Signs:**
    - **General Anaemia Symptoms & Signs.**
- **Investigations:**
  - **Iron Studies:**
    - ↓Serum Iron
    - ↓TIBC
    - Normal Serum Ferritin
  - **B12/Folate**
  - **Blood Film**
- **Treatment:**
  - **Treat Underlying Chronic Inflammation/Infection**
    - Corticosteroids (↓Inflammation)
  - **Correct Anaemia:**
    - Exogenous EPO (↑Erythropoiesis)

OTHER NORMOCYTIC ANAEMIAS:

- **Aetiologies:**
  - *Acute Blood Loss*
  - *Anaemia of Chronic Disease*
  - *Marrow Failure*
  - *Renal Failure*
  - *Pregnancy (Spurious)*

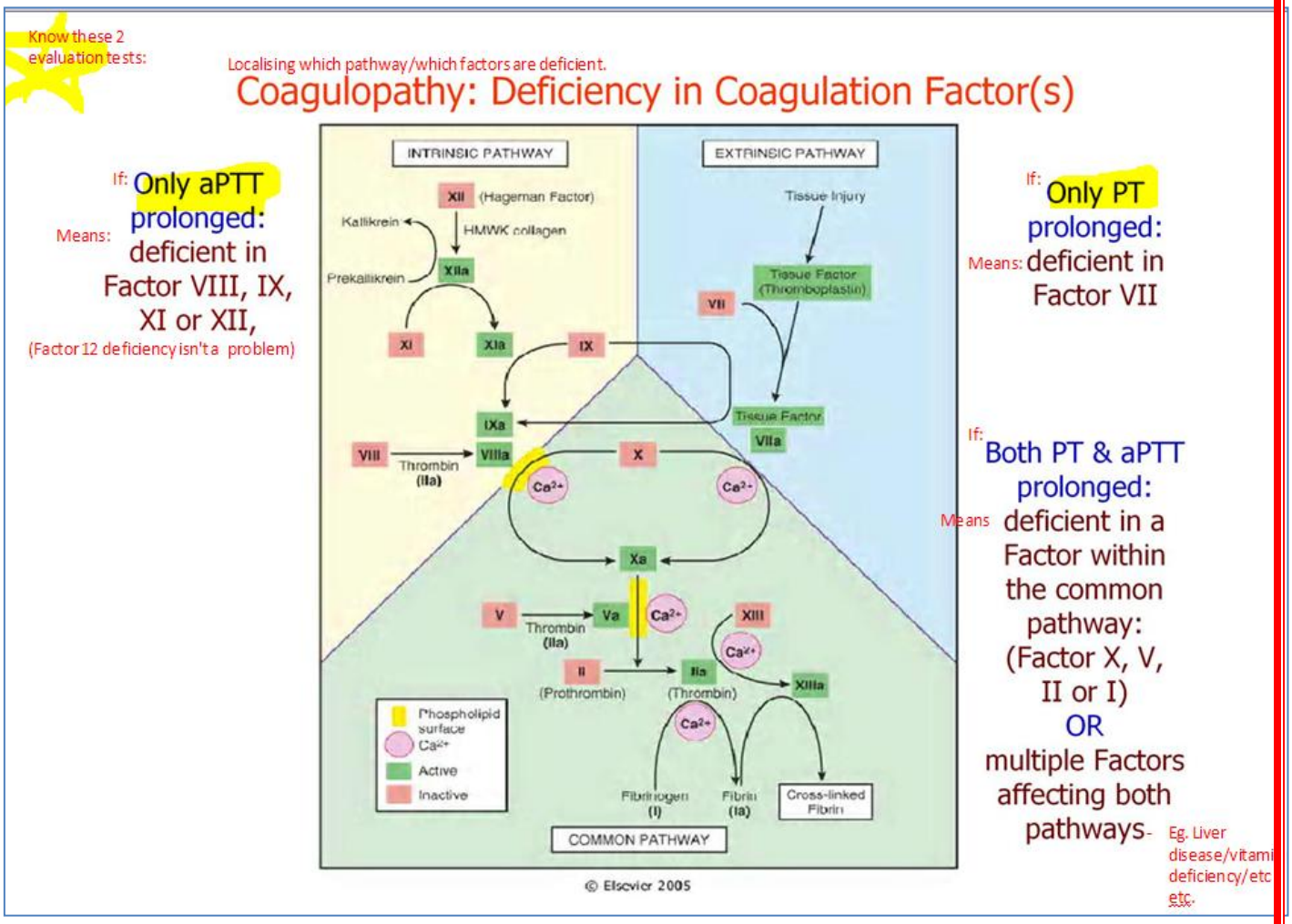
HAEMATOLOGY Pathology:
BLEEDING DISORDERS

1. Bleeding Disorders:

- **Vascular Disorders:**
  - Abnormalities in Blood Vessel Structure or Perivascular Connective Tissue
  - Inherited or Acquired
- **Thrombocytopenia:**
  - Due to ***deficient number of platelets.***
    - ↓ Platelet Production
    - ↑ Platelet Destruction
    - ↑ Platelet Consumption (in large injuries/burns)
- **Defective Platelet Function:**
  - There are enough platelets, but not working properly.
  - May be Inherited (rare)...OR
  - Acquired: (eg. From Aspirin/other blood thinners)
- **Von Willebrand's Deficiency:**
  - Ordinarily vWF is necessary for platelet adhesion.
  - :. Deficiency → Poor platelet plug formation
- **Coagulopathy = Defective Coagulation:**
  - **Due to deficiency in 1 or more Coag. Factors**
  - **Heriditary Factor Deficiencies:**
    - **Haemophilia A: Factor VIII Deficiency:**
      - Sex Linked Recessive (Only Affects Males)
      - **Treatment - Recombinant** clotting factors
    - **Haemophilia B: Factor IX Deficiency:**
      - Sex Linked Recessive (only affects males)
      - **Treatment - Recombinant** clotting factors
    - **Other deficiencies (Factors V, VII, X, XI & XIII) Rare.**
      - Just know they exist.
  - **Acquired:**
    - **Vitamin K Deficiency (Factors II, VII, IX, X)**
      - Due to Diet / Malabsorption / Warfarin
    - **Chronic Liver Disease:**
      - Reduced synthesis of Factors II, VII, IX & X
    - **DIC - Disseminated Intravascular Coagulation:**
      - AKA. Consumptive Coagulopathy
      - Generalised micro-clot formation → ↑Consumption of Platelets & Factors.

Investigations:

- **FBC –** (↓Platelet Count = Thrombocytopenia, Platelet Morphology → Dysfunction)
- **Tests of Coagulation-Factor Function:**
  - **Prothrombin Time (PT):**
    - *Time taken for plasma to clot after addition of tissue factor (Factor III)*
    - INR (International Normalized Ratio) is derived from PT → Universal measurement.
  - **INR (International Normalized Ratio)**
    - Typically Warfarin Monitoring (aim for INR 2-3)
  - **Activated Partial Thromboplastin Time (aPTT):**
    - *Time taken for plasma to clot after addition of phospholipids*
    - Measures factors XII, XI, IX, VIII, X, V, II (Prothrombin) and I (fibrinogen).
    - 45sec+ = One/more of above factors are deficient.
  - **Thrombin Time:**
    - Measures:
      - The conversion of Fibrinogen → Fibrin.
      - Any deficiency of fibrinogen
      - Any inhibition of thrombin.



NB: Once the defective pathway is identified, there are other tests for specific factors to help narrow it down.

HAEMATOLOGY Pathology:
CLOTTING DISORDERS

1. Thrombotic Disorders:

- NB: Thrombosis = inappropriate formation of Platelet & Fibrin Clots
  - **Arterial Thrombosis:**
    - **Atherosclerotic Plaque in Arterial walls → Arterial Thrombosis.**
  - **Venous Thrombosis:**
    - Occur Mostly in Lower Extremities (due to gravity pooling blood)
    - **Due to Acquired Hypercoagulable States:**
      - **High-Dose Oestrogen Therapy:**
        - ↑Plasma levels of Coag. Factors
        - ↓ Antithrombin & Tissue-Plasminogen-Activator
      - **Major Surgery/Trauma:**
        - Due to high tissue damage
        - Immobility after surgery (Venous Stasis)
      - **Pregnancy & Post-Partum (↑Levels of Coag. Factors during pregnancy)**
      - **Sepsis (bacterial infection → widespread damage to endothelium)**
      - **Heparin-Induced Thrombocytopaenia** (some people on heparin develop antibodies to their own platelets)
      - **Blood Stasis**:.....from:
        - Heart Failure (not pumping adequately)
        - Stroke
        - Prolonged Immobility
        - Nephrotic Syndrome (loss of Coag. Factors through Urine)
        - Varicose Veins

Investigations:

- **Complete Blood Count ...&...Erythrocyte Sedimentation Rate**
- **Prothrombin Time (PT)** – (Short)
- **Activated Partial Thromboplastin Time (aPTT)** – (Short)
- If Both PT & aPTT are Abnormal, *Probably due to:*
  - *Liver disease*
  - *Vit. K Deficiency……..or*
  - *Oral Anticoagulants*
- **INR –** If on Warfarin (Dose too low)

Management:

- **Heparin (INJECTABLE):**
  - Fast-acting
  - How?: Stimulates Antithrombin Activity
  - 2 Types:
    - Standard Heparin – (Requires Monitoring)
    - Low Molecular-Weight Heparin – (No need for Monitoring; but Expensive)
- **Warfarin (ORAL):**
  - Most common oral Coag.
  - How?: Vitamin K Antagonist (Decreases Factors II, VII, IX & X)
  - NB: Contraindicated in Pregnancy – (Teratogenic)
  - Monitored by PT / INR
- **Fibrinolytics – (Tissue Plasminogen Activator & Streptokinase):**
  - Degrade Thrombi
  - Used Systemically...or...injected directly into thrombus.
- **Antiplatelet Drugs:**
  - Eg. Aspirin
  - Eg. Clopidogrel

Combined Bleeding & Thrombotic Disorder

Disseminated Intravascular Coagulation

Secondary to severe disease, many systemic causes (sepsis, burns, trauma, malignancy etc). Widespread endothelial & tissue damage & exposure tissue factor causes activation of coagulation (multiple micro-thrombosis) and consumption of coagulation factors and platelets which leads to bleeding. Signs: thrombosis, embolism, haemorrhage. Diag: low platelets, low fibrinogen, prolonged Thrombin time, high FDPs eg D-dimer test, PT and aPTT may be prolonged, red cell fragmentation. Treat: underlying cause, fresh plasma, cryoprecipitate, heparin etc.

HAEMATOLOGY Pathology:
HAEMOCHROMATOSIS

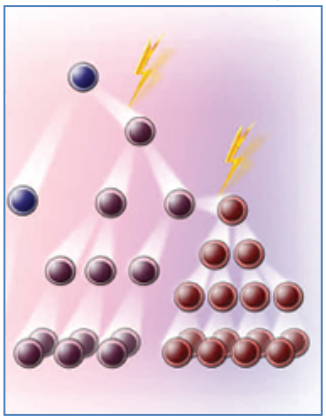
Haemochromatosis:

- **Aetiology:**
  - **(Iron Overload in the Body Due to):**
    - **Primary – (**Heriditary Mutation in HFE Gene → ↑↑Iron Absorption)
    - **Secondary – (**Repeated Transfusions, Excess Iron Supplements/Dietary Iron)
- **Pathogenesis:**
  - → Iron Deposition in multiple Organs (Skin/Joints/Liver/Pancreas/Pituitary)
    - **Liver** - Cirrhosis
    - **Heart** - Cardiomyopathy
    - **Endocrine Glands:**
      - Testicular Failure
      - Pituitary Gland
      - Tanning of the skin
      - Diabetes (Due to Islet Cell Failure)
    - **Joints** - Arthritis (Iron Deposition in the Joints)
- **Clinical Features:**
  - **Symptom Profile:**
    - **Initially Asymptomatic**
    - **Early Symptoms:**
      - Fatigue
      - Arthralgia
      - Loss of Libido
    - **Later Symptoms:**
      - Skin Bronzing
      - Abdo Pain, Hepatomegaly
      - Liver Cirrhosis
      - Hypogonadism (from Pituitary Dysfunction)
- **Diagnosis:**
  - **Iron Studies – (**↑Serum Ferritin & Iron Levels, ↑Transferrin Saturation & ↓TIBC)
  - **+ve HFE Genetic Mutation**
  - **LFTs – (**Cirrhosis**)**
  - **Echocardiogram – (**Cardiomyopathy**)**
- **Treatment:**
  - **Venesection**
  - **Low Iron Diet**

Leukaemias

What Are Leukaemias?:

- **= Myeloproliferative & Lymphoproliferative Disorders**
- ***=A Type of Cancer*** *Caused by Unregulated Proliferation of Abnormal 'White Cells' from a* ***Mutant*** *Haematopoietic Stem Cell.*
  - Successive generations of cells from that ***Mutant*** *Haem. Stem Cell* → 'Clonal Expansion'
  - NB: Disease occurs when sufficient excess in Leukocytes.

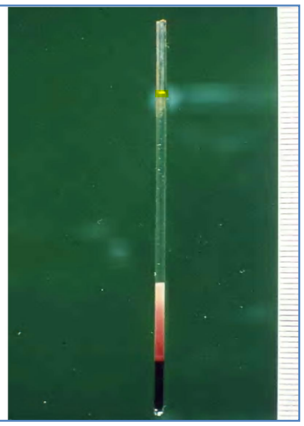


- **Mutation** – Genetic Alteration within a *Single Myeloid (Bone Marrow)OR Lymphoid Tissue.*
  - **Chromosomal Translocations:**
    - ***Philadelphia Chromosome:**
      - *#1 Cause of:* → *Chronic Myeloid Leukaemia
  - **Chromosomal Deletions/Additions:**
    - ***Monosomy 7:**
      - *#1 Cause of:* → *Acute Myeloid Leukaemia
  - **Point Mutations**
  - **Gene Amplification:**
    - **Changes in Proto/Anti-Oncogenes:**
      - Oncogenes: Code for proteins involved in cell proliferation/differentiation.
      - Abnormal Proto/Anti-Oncogenes → Cancers (ie. Leukaemia)
      - Eg. A Hypermorphic Mutation in an *Oncogene* → Hyperactive Proliferation
      - Eg. A Hypomorphic Mutation in a *Tumour-Suppressve* Gene → Hyperactive Proliferation

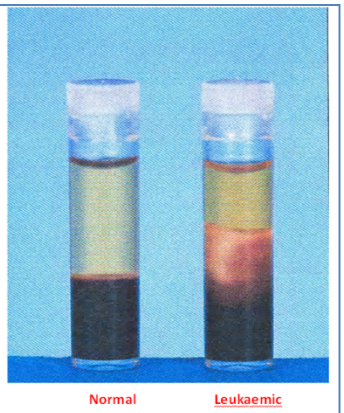
Result:

- Extreme numbers of White Cells in blood → **Altered Haematocrit:**
  - Huge Buffy Coat (of WBCs – generally abnormal)
  - Low Proportion of RBCs (Results in Anaemia)

Haematocrit – acute leukaemia



Blood sample – increased size of "buffy coat"



Risk Factors:

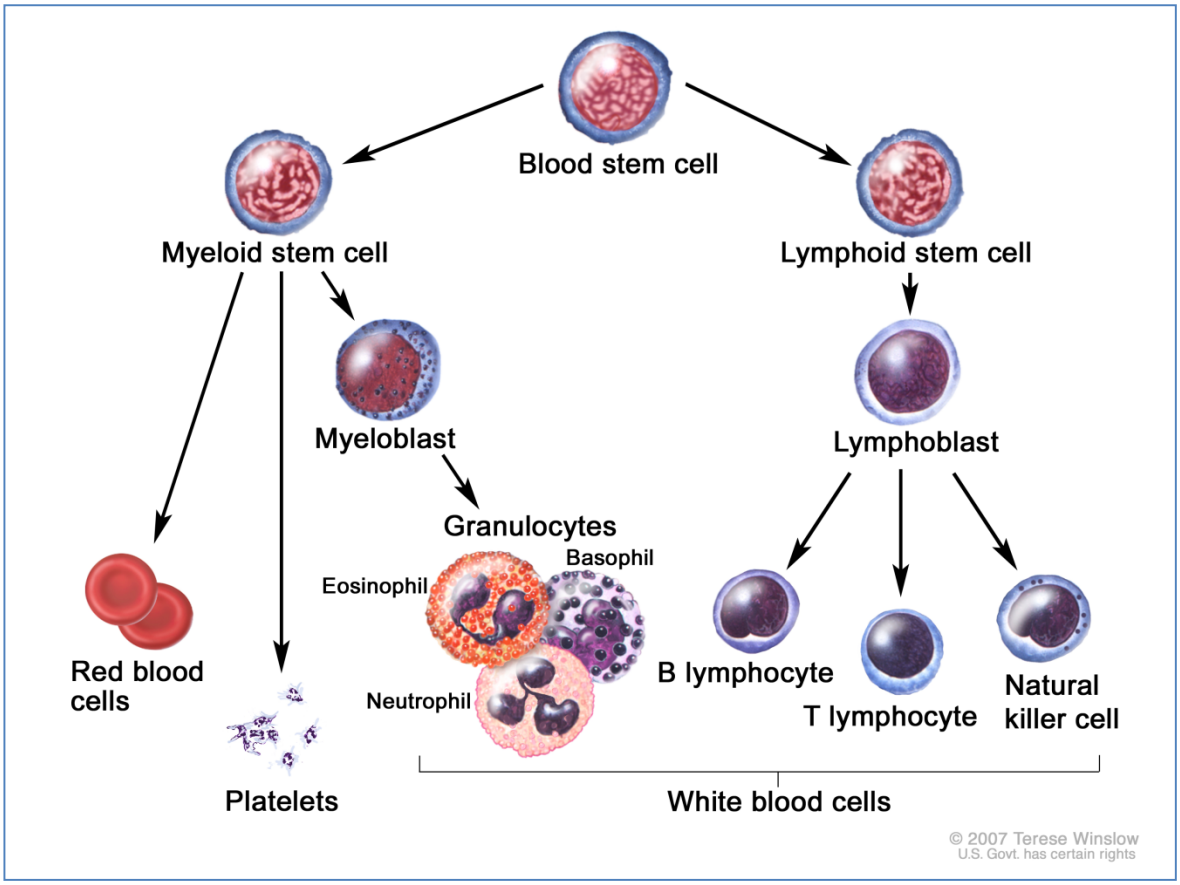
- **Radiation Exposure –** Nuclear/X-Ray/Microwave
- **Previous Chemotherapy –** Particularly Alkylating Agents
- **Genetic –** eg. Down's Syndrome
- **Occupational Chemical Exposure** – Benzene/Other Aromatic Organic Solvents
- **Viral Infection**

Classification of Leukaemia:

- ***Acute* OR *Chronic***
- ***Myeloid* OR *Lymphoid***
- ***Other***

    - **Acute:**
        - **Myeloid:**
            - Acute Myeloid Leukaemia:
        - **Lymphoid:**
            - Acute Lymphoblastic Leukaemia
    - **Chronic:**
        - **Myeloid:**
            - Chronic Myeloid Leukaemia
        - **Lymphoid:**
            - Chronic Lymphocytic Leukaemia
    - **Other:**
        - **Hairy-Cell Leukaemia**
        - **Prolymphocytic Leukaemia**
        - **T-Cell Leukaemic Lymphoma**

REVISION OF BLOOD CELL LINEAGES:



Acute Myeloid Leukaemia:

- **Characterised By:**
  - Rapid proliferation of *Malignant Cells* → Accumulate in the bone marrow
- **Most Common in ADULTS** –↑Incidence with Age
- **Subdivided in 8 Types** – Defined by **"FAB-Scheme"** (French/American/British)
  - Based on the *Type of Cell* from which the leukaemia developed + Maturity
  - 8 Groups = 'M0' → 'M7'
- **Clinical Signs:**
  - **Anaemia – Low [Hb] (due to ↓RBCs)**
    - Fatigue
    - Shortness of Breath
  - **Neutropaenia – (Low Neutrophils)**
    - ↑Malignant White Blood Cells + ↓Normal White Blood Cells
    - Susceptible to Infection
  - **Thrombocytopaenia – (Low Platelets)**
    - Easy Bruising/Bleeding
- **Reasons for Clinical Signs:**
  - Rapid proliferation of *Malignant Cells* → Accumulate in the bone marrow
    - → 'Packs Out' the bone→ interfere with the production of normal blood cells
  - Hence, Symptoms Caused by **Replacement of Normal Bone Marrow with Leukaemic Cells**
    - **→ ↓RBCs**
    - **→ ↓*Normal* White Blood Cells**
    - **→ ↓Platelets**
- **Diagnosis:**
  - **Complete Blood Count:**
    - Excess Abnormal Leukocytes
    - Blast Cells (Big, Immature Cells)
    - Anaemia
    - Thrombocytopaenia
  - **Bone Marrow Aspiration/Biopsy:**
    - Required for *Definitive* Diagnosis
    - Presence of Blast Cells
  - **Cytogenetics:**
    - Testing for Chromosomal Translocations
  - **Cytochemistry:**
    - Using *Cytochemical Stains* to Differentiate between AML & ALL
      - Stains = Myeloperoxidase & Sudan Black Stain
        - AML – Positive with Both Stains.
        - ALL – Negative with Both Stains.
- **Treatment:**
  - **Chemotherapy**
  - **Haematopoietic Stem Cell Transplant**

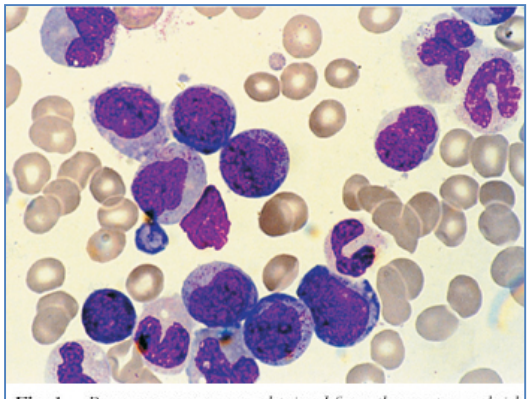
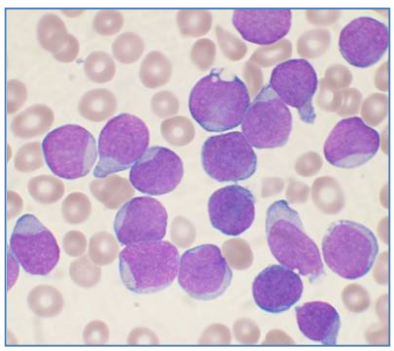


Fig. 1 – Bone marrow smear obtained from the acute myeloid leukaemia subtype M2 case at diagnosis showing blast cells, promyelocytes, myelocytes and neutrophils (Romanovsky, 100x)

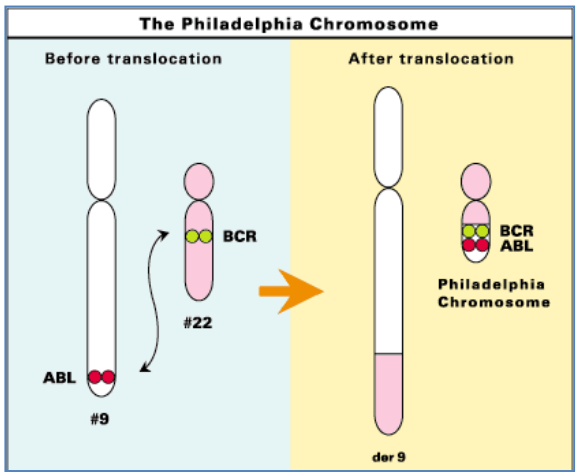
Acute Lymphoblastic Leukaemia:

- **Characterised By:**
  - Excess B-Lymphoblasts. (B-Lymphocyte Precursors)
  - Malignant, immature white blood cells continuously multiplying in the bone marrow.
  - A.L.L. crowds out normal cells in the bone marrow, and spreads (metastases) to other organs.
  - Can be fatal in weeks to months if left untreated.
- **Most Common in CHILDREN** ('Children's Leukaemia')
  - Peak incidence at 4-5 years of age
- **Subdivided Based on:**
  - Morphology
  - Cell-Surface Antigens
- **Clinical Signs:**
  - **Anaemia – Low [Hb] (due to ↓RBCs)**
    - Fatigue
    - Shortness of Breath
  - **Thrombocytopaenia – (Low Platelets)**
    - Easy Bruising/Bleeding
  - **Frequent Fevers/Infections**
  - **Weight-Loss/Loss of Appetite**
  - **Bone/Joint Pain**
  - **Enlarged Lymph Nodes**
  - **Enlarged Liver/Spleen**
  - **Oedema in Lower Limbs**
- **Reasons for Clinical Signs:**
  - Lack of normal and healthy blood cells due to crowding out by malignant and immature WBC's.
  - Therefore, symptoms due to malfunctioning of:
    - Red Blood Cells
    - Leukocytes
    - Platelets
- **Diagnosis:**
  - **Physical Examination**
  - **Complete Blood Count:**
    - Excess Abnormal Leukocytes
    - Blast Cells (Big, Immature Cells)
    - Anaemia
    - Thrombocytopaenia
  - **Bone Marrow Aspiration/Biopsy:**
    - Required for *Definitive* Diagnosis
    - Presence of Blast Cells
  - **Cytogenetics:**
    - Testing for Chromosomal Translocations
      - Particularly for the 'Philadelphia Chromosome'
  - **Cytochemistry:**
    - Using *Cytochemical Stains* to Differentiate between AML & ALL
      - Stains = Myeloperoxidase & Sudan Black Stain
        - AML – Positive with Both Stains.
        - ALL – Negative with Both Stains.
- **Treatment:**
  - **Chemotherapy**
  - **Radiotherapy**



Chronic Myeloid Leukaemia:

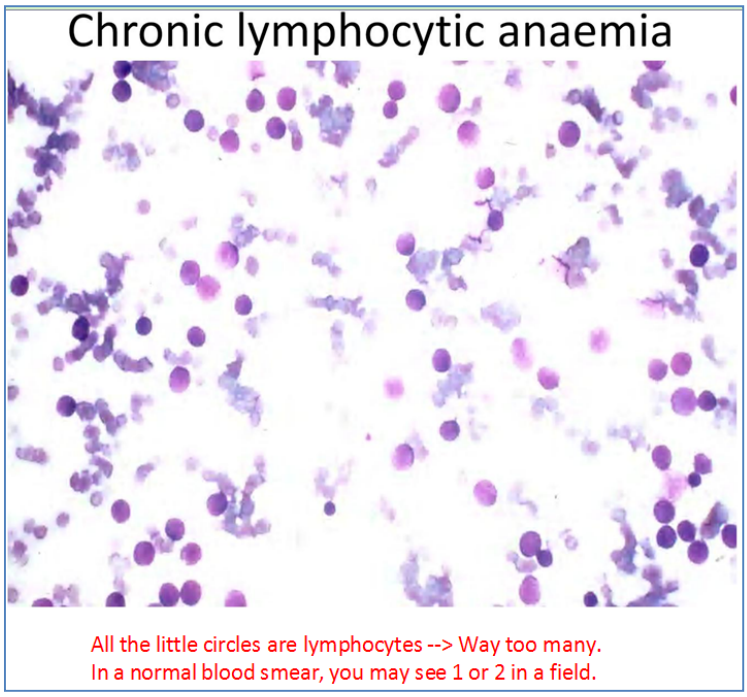
- **Characterized By:**
  - - A characteristic chromosomal translocation called the Philadelphia chromosome. →
    - High, Unregulated growth of myeloid cells in the bone marrow →accumulation in the blood.
    - ↑↑Proliferation of Mature & Immature Granulocytes (neutrophils/eosinophils/basophils).
- **Most Common in ADULTS:**
  - Peak incidence (50-60yrs)
- **Clinical Signs:**
  - **Often Asymptomatic** (Usually detected by routine blood tests)
  - **Anaemia – Low [Hb] (due to ↓RBCs)**
    - Fatigue
    - Shortness of Breath
  - **Thrombocytopaenia – (Low Platelets)**
    - Easy Bruising/Bleeding
  - **Malaise** (general feeling of being unwell)
  - **Mild Fever**
  - **Gout** (Metabolic Arthritis – Due to ↑[Uric Acid] in blood)
- **Phases:**
  - **Chronic Phase:**
    - See above for symptoms
  - **Accelerated Phase:**
    - Progression of CML → can change to an Acute Form
    - 'Blast Crisis' is imminent.
  - **Blast Crisis:**
    - Fatal Acute Leukaemic Phase
    - Final phase in the evolution of CML
    - Behaves like an acute leukaemia
    - Rapid Progression + Short survival.
    - Requires Immediate Bone Marrow Transplant to Survive.
- **Diagnosis:**
  - **Ultimately by Detecting the 'Philadelphia Chromosome'**
    - Via Cytogenetics (Testing for Chromosomal Translocations)
  - **Bone Marrow Aspiration/Biopsy:**
    - Presence of Blast Cells
    - Not enough to diagnose.
- **Treatment:**
  - **Chronic Phase:**
    - Tyrosine Kinase Inhibitors
  - **Blast Crisis:**
    - Requires Immediate Bone Marrow Transplant to Survive.



Results when part of Ch.9 switches places with part of Ch.22. Forms an extra-long Ch.9,
& an extra-short Ch.22 = The Philadelphia Chromosome. – Contains the abnormal gene-fusion.

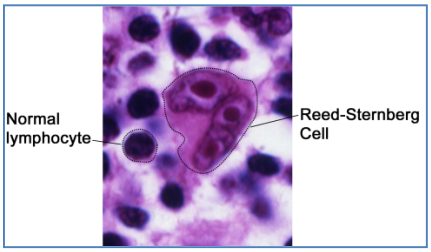
Chronic Lymphocytic Leukaemia:

- **Characterized By:**
  - Overproliferation of Mutated B-Cells → Can't Fight Infection.
  - The cells accumulate mainly in the bone marrow and blood.
- **Most Common in ADULT MALES:**
  - Peak incidence (50-60yrs)
- **Clinical Signs:**
  - Most diagnosed without symptoms via routine blood test →returns high white cell count
  - Advances To:
    - Swollen lymph nodes
    - Splenomegaly
    - Hepatomaegaly
    - Eventually Anaemia and Infections.
- **Diagnosis:**
  - Most diagnosed without symptoms via routine blood test →returns high white cell count
    - CLL is usually first suspected by the presence of a lymphocytosis, an increase in one type of the white blood cell, on a complete blood count (CBC) test.
- **Treatment:**
  - Early CLL is not treated
  - CLL treatment is only taken when clinical symptoms/blood counts indicate progression to a point where it may affect the patient's quality of life.
  - Late CLL is treated with chemotherapy and monoclonal antibodies.



Malignant Lymphomas:

- **2 Groups:**
  - **Hodgkin's Lymphoma:**
    - **Characterized By:**
      - The presence of Reed-Sternberg cells (RS cells).
        - (Bi/Multi-Nucleated Cells derived from lymphoid cells)
      - & the spread of disease from one lymph node group to another →the development of systemic symptoms with advanced disease.
    - **Most Common In Males:**
      - Young Adulthood (15-35)
      - Late Adulthood (55+)
    - **Clinical Signs:**
      - Asymmetrical & Painless Lymphadenopathy (Lymph Node Swelling)
      - Fever
      - Sweating
      - Weight Loss
      - Fatigue
    - **Diagnosis:**
      - Definitive diagnosis is by lymph node biopsy (Usually excisional biopsy with microscopic examination).
      - →Presence of 'RS Cells'
    - **Treatment:**
      - Radiation Therapy OR
      - Chemotherapy
        - Depending on Age.



  - **Non-Hodgkin's Lymphomas:**
    - **What Are They?:**
      - Diverse group of Haematologic Cancers, Encompassing Any Lymphoma *other than* Hodgkin's Lymphoma.
      - Complicated Classification.
      - Occur At Any Age.
      - May be Aggressive/Benign
    - **Clinical Signs:**
      - Initially Painless Lymphadeopathy (Mainly in Cervical Region)
      - Subsequent signs depends on infiltration of other body systems.
    - **Diagnosis:**
      - Physical Exam
      - Blood Tests
      - Bone Marrow Test
      - CT-scans
      - Lymph node Biopsy
    - **Treatment:**
      - Chemotherapy

Multiple Myeloma:

- **Characterized By:**
  - Proliferation of ***Plasma Cells*** in the bone marrow
  - → Overproduction of Immunoglobulins
- **Clinical Signs:**
  - Often Asymptomatic
  - However:
    - Excess Immunoglobulins → Blocks + Damages Renal Tubules
    - Excess Immunoglobulins → Lyses Bone → Bone Pain
      - Bone Lysis → Anaemia → Lethargy.
      - Bone Lysis → Elevate Blood-Ca^{+}
- **Diagnosis:**
  - protein electrophoresis of the blood and urine → For Presence of 'Paraprotein' (an Abnormal Immunoglobulin produced by Tumor Plasma Cells)
  - A bone marrow biopsy is usually performed to estimate the percentage of bone marrow occupied by plasma cells.
- **Treatment:**
  - Chemotherapy
  - Stem-Cell Transplantation

Myelodysplastic Syndromes (AKA "Pre-Leukaemia"):

- Diverse Group of Haematological Conditions:
- **Characterised By:**
  - *Ineffective Production* (Dysplasia) of Myeloid Blood Cells
- **Most Common in Elderly**
  - 60-75
- **Clinical Signs:**
  - **Bone-Marrow Failure → Abnormalities of All 3 Myeloid Cell Lines:**
    - ↓RBCs → Anaemia
    - ↓Granulocytes → Neutropaenia
    - ↓Platelets → Thrombocytopaenia
  - **Often leads to Acute Myeloid Leukaemia**
- **Diagnosis:**
  - Excessive Bruising/Bleeding
  - Infections
  - Abnormal RBCs
  - Abnormal WBCs
  - Chromosome Abnormalities
- **Treatment:**
  - Chemotherapy

SideNote:

Polycythaemia:

- **2 Types:**
  - **Absolute Polycythemia:** An increase in red cell mass caused by increased erythropoiesis, which may occur as a compensatory physiologic response to tissue hypoxia or as the principal manifestation of polycythemia vera.
  - **Relative Polycythemia:** A decrease in plasma volume without change in red blood cell mass so that the erythrocytes become more concentrated (elevated hematocrit), which may be an acute transient or a chronic condition.

HAEMATOLOGY Pathology:
LEUKAEMIAS

LEUKAEMIAS - General:

Type of Leukaemia	Distinguishing Features
ALL – Acute Lymphoblastic Leukaemia	Children Good Prognosis Small Lymphoblasts, Small Cytoplasm, No Granules/Nucleoli
AML – Acute Myeloid Leukaemia	Adults Poor Prognosis (2mths if untreated) Gum Hypertrophy "Auer Rods" in AML Myeloblast Cells Big Myeloblasts, Big Cytoplasm, Granules, Nucleoli.
CLL – Chronic Lymphocytic Leukaemia	Elderly Commonest Leukaemia Insidious Onset Good Survival (9yrs) but NO Cure "Smear Cells" on blood film
CML – Chronic Myeloid Leukaemia	Adults Philadelphia Chromosome in 80% Good Prognosis with Glivec (Imatinib) 3 Phases: Chronic, Accelerated, Blast Crisis. Marked Splenomegaly

(NB: Myeloids are ALWAYS in Adults; Lymphoids are EXTREMES of Age)
(All are ~Good Prognosis EXCEPT AML)
(CML = Philadelphia Chromosome & Tri-Phasic with "Blast Crisis")

- **ALL - ACUTE LYMPHOBLASTIC LEUKAEMIA:**
  - **Aetiology:**
    - Genetic / Environmental
  - **Pathology:**
    - Malignancy of ***Lymphoblasts*** → Uncontrolled Proliferation → BM Failure → Metastases
      - Bone, Liver, Spleen, Lymph Nodes
  - **Clinical Features:**
    - **Most Common in Young Children (4-5yrs)**
    - **Good Prognosis (70-90% Cure Rate) (Low Mortality)**
    - **Signs & Symptoms:**
      - **Bone Pain** (Especially sternum)
      - **Marrow Failure →**
        - **↓Hb → Anemia** → Pallor, weakness, fatigue, dyspnea.
        - **↓Platelets → Thrombocytopenia** → Bruising & bleeding
        - **↓WCC → Neutropenia** → Infections
      - **Organomegaly (**Liver, Spleen**)**
      - **Lymphadenopathy** (Incl. Mediastinal)
  - **Diagnosis:**
    - **FBC** – ↑WCC, ↓Hb, ↓PLTs
    - **Blood Film** - Characteristic ***Lymphoblast*** Cells
    - **BM Biopsy** - Characteristic ***Lymphoblast*** Cells
    - **CXR/CT** – Mediastinal/Abdominal Lymphadenopathy
  - **Treatment:**
    - **Supportive –** Transfusions/Fluids
    - **IV Antibiotics -** + Antivirals/Antifungals
    - **Chemotherapy –** Aim for Remission
    - **Allogeneic Marrow Transplant**

- **AML - ACUTE MYELOID LEUKAEMIA:**
  - **Aetiology:**
    - Genetic / Environmental
    - Or Progression from Myelodysplastic States
  - **Pathology:**
    - Malignancy of ***Myeloblasts*** →Uncontrolled Proliferation → BM Failure → Metastases
  - **Clinical Features:**
    - **Poor Prognosis (High Mortality)**
    - **Most Common in ADULTS** –↑Incidence with Age
    - **Signs & Symptoms:**
      - **Bone Pain** (Especially sternum)
      - **Marrow Failure →**
        - **↓Hb → Anemia** → Pallor, weakness, fatigue, dyspnea.
        - **↓Platelets → Thrombocytopenia** → Bruising & bleeding
        - **↓WCC → Neutropenia** → Infections
      - **Organomegaly (**Liver, Spleen**)**
      - **Lymphadenopathy** (Incl. Mediastinal)
      - **Gum Hypertrophy**
  - **Diagnosis:**
    - **FBC** – ↑WCC, ↓Hb, ↓Plts
    - **Blood Film** - Characteristic ***Myeloblast*** Cells
    - **BM Biopsy** - Characteristic ***Myeloblast*** Cells with pathogonomic **"Auer Rods"**
    - **CXR/CT** – Mediastinal/Abdominal Compression & Infection
  - **Treatment:**
    - **Supportive –** Transfusions/Fluids
    - **IV Antibiotics -** + Antivirals/Antifungals
    - **Chemotherapy –** Aim for Remission
    - **Allogeneic Marrow Transplant**

- **CLL - CHRONIC LYMPHOCYTIC LEUKAEMIA:**
  - **Aetiology:**
    - Genetic Sensitivity
  - **Pathology:**
    - Malignancy of ***Neoplastic, Mature, Poorly-Functioning B-Cells*** → Slow BM Failure→ & Slow Metastasis
  - **Clinical Features:**
    - ***The Commonest Leukaemia, Mainly in Elderly (50-60yrs).***
    - ***Good Survival – 9yr Median Survival – But NO CURE*** (Death due to infection, not mets)
    - **Symptoms:**
      - **Typcally Asymptomatic @ Dx – 60%. (Dx on routine blood test)**
      - BM Failure – (Anaemia, Recurrent Infection, Bruising)
      - If Severe – Weight Loss, Sweats, Anorexia.
    - **Signs:**
      - Lymphadeopathy (Esp. Cervical) Enlarged, Rubbery, *Non-Tender*.
      - Organomegaly
  - **Diagnosis:**
    - **Blood Count & Film – (**↑↑Lymphocytosis, Anaemia, Neutropaenia, Thrombocytopaenia**)**
  - **Treatment:**
    - **Early CLL is not treated**
    - ***CLL is only Treated when symptoms affect Quality of Life.***
    - → **IV-Ig. –** For Infections; **Chemotherapy/Radiotherapy –** Palliative
    - **(Stem Cell Transplant – Curative)**

- **CML - CHRONIC MYELOID LEUKAEMIA:**
  - **Aetiology:**
    - **Genetic (Philadelphia Chromosome - >80%)**
  - **Pathology:**
    - **Myeloid Prolipheration in BM & Blood.**
    - ***3 Phases:***
      - ***Chronic Phase*** (Insidious, few/no symptoms)
      - ***Accelerated Phase*** (Fever, Increasing BM Failure Symptoms, ↑Splenomegaly)
      - ***Blast Crisis*** **(**Features of Acute Leukaemia → Death from Sepsis/Bleeding):
  - **Clinical Features:**
    - **Middle-Age (40-60yrs)**
    - **Symptoms:**
      - **Often Asymptomatic** (Usually detected by routine blood tests)
      - **BM Failure:**
        - **Anaemia – Low [Hb] (due to ↓RBCs)**
        - **Thrombocytopaenia – (Low Platelets)**
        - **Neutropaenia – (Infection)**
      - **Malaise** (general feeling of being unwell)
      - **Fever, Weight Loss, Fatigue**
      - **Abdo Discomfort** (**Splenomegaly**)
    - **Signs:**
      - **Organomegaly** in >75%
      - Anaemia/Bruising
    - **Diagnosis:**
      - **FBC/Blood Smear** - ↑↑WCC with ↑All Myeloid Cell Types
      - **Marrow Biopsy** - Hypercellular Marrow
      - **Molecular Genetics** - Philadelphia Chromosome
    - **Treatment:**
      - **Chemotherapy** – ***Glivec (Imatinib)*** **– A Tyrosine Kinase Inhibitor**
      - *****Blast Crisis*** Requires Immediate Bone Marrow Transplant to Survive

HAEMATOLOGY Pathology:
LYMPHOMAS

HODGKIN'S LYMPHOMA (15%):

- **Aetiology:**
  - **Idiopathic**
  - **Risk Factor = EBV (Infective Mononucleosis)**
- **Pathology:**
  - **Malignant Lymphocytes** → Accumulate in Lymph Nodes, Peripheral Blood & Other Organs
- **Clinical Features:**
  - **Bimodal Distribution -** Young Adult (20yrs), or Elderly (>50yrs)
  - **Good Prognosis** – High Cure Rate
  - **Signs & Symptoms:**
    - ***Painless Lymphadenopathy** – Non-Tender, Rubbery (Neck, Axillary)
    - **Systemic "B" Symptoms –** (Fever, Night Sweats, Weight Loss, Fatigue)
    - **Splenomegaly/Hepatomegaly**
    - **Pathogonomic Symptoms:**
      - Pruritis
      - Alcohol Induced Lymph Node Pain.
  - **Diagnosis:**
    - ***LN Biopsy -** Presence of ***Reed-Sternberg Cells***
    - ***BM Biopsy** – Presence of ***Reed-Sternberg Cells***
    - **CT Chest/Abdo/Pelvis** (Look for Mets).
  - **Treatment:**
    - (Depends on Staging; Curative Intent)
    - **Radiotherapy +/- Chemotherapy**
  - **Complications:**
    - **SVC obstruction** (due to Mediastinal Masses) → ↑JVP, Facial Plethora, Dyspnoea.

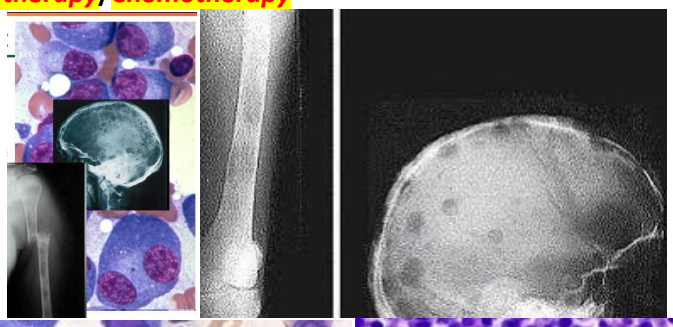
NON-HODGKIN'S LYMPHOMA (85%):

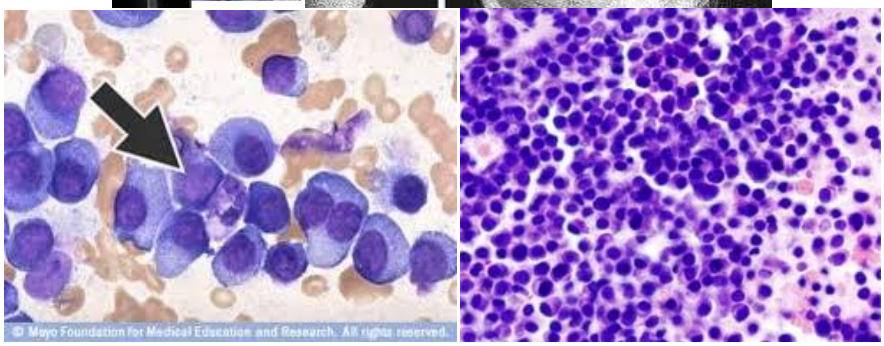
- **Aetiology:**
  - **Post-Viral Infections** – ***HTLV-1, EBV, HHV8, HIV, H.pylori***
  - **Environmental Toxins** – ***Pesticides, Organic Solvents***
- **Pathology:**
  - **Malignant Lymphocytes** → Accumulate in Lymph Nodes, Peripheral Blood & Other Organs
- **Clinical Features:**
  - ***POOR Prognosis – 5yrs for treated pts.**
  - **Signs & Symptoms:**
    - **Painless Lymphadenopathy** – Non-Tender, Rubbery (Neck, Axillary)
    - **Systemic "B" Symptoms –** (Fever, Night Sweats, Weight Loss, Fatigue)
    - **Splenomegaly/Hepatomegaly**
    - **Metastases** → GIT, Lungs, Brain, Testes, Thyroid & Skin.
  - **Diagnosis:**
    - **BM Biopsy**
    - **Lymph Node Biopsy**
    - **CXR/CT** – for Staging
  - **Treatment:**
    - (Depends on Staging)
    - **Radiotherapy may be Curative if Localised Disease.**
    - **Chemotherapy in Diffuse Disease**

HAEMATOLOGY Pathology:
MULTIPLE MYELOMA

MULTIPLE MYELOMA:

- **Aetiology:**
  - Malignancy (Overproduction) of *FUNCTIONING* **Plasma Cells** in Bone Marrow
- **Pathology:**
  - **Over-Proliferation of Plasma Cells** →
    - → Only Produces ***Monoclonal*** Igs → **Recurrent Infections**
    - + → Increased **Osteoclastic Activity** → **Lytic Bone Lesions** → Bone Pain.
- **Clinical Features:**
  - **Elderly, Males.**
  - **Symptoms:**
    - **Bone Pain** (Typically Back Pain – Vertebral Involvement)
    - **BM Failure -** Anaemia/Bleeding/Recurrent Infections
  - **Signs:**
    - **Pathological Fractures**
    - **Hypercalcaemia**
    - **BM Failure** → Aaemia/Bleeding/Infection
    - **Ig Deposition in Renal Tubules** → Renal Impairment
    - **Recurrent Infections**
  - **Diagnosis:**
    - **FBC & Blood Film – (**↑↑Plasma Cells (BM & Peripheral Blood)**)**
    - **↑ESR/CRP**
    - **UEC – (**↑Ca**)**
    - **CT/MRI/XR** – Lyic Bone Lesions
    - **BM Biopsy** – Infiltration of BM by Plasma Cells
  - **Treatment:**
    - Supportive Treatment – Transfusions/Antibiotics
    - **Allogeneic *BM Transplant***
    - ***Bisphosphonates Inhibit Osteoclast Activity***
    - ***Radiotherapy*** / ***Chemotherapy***

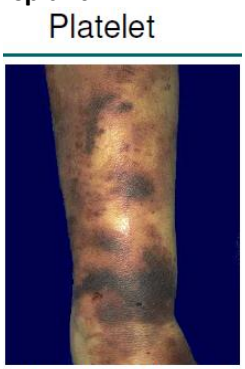




HAEMATOLOGY Pathology:
MYELOPROLIFERATIVE DISEASE

MYELODYSPLASTIC (*PRELEUKAEMIC*) SYNDROMES:

- (As opposed to myeloproliferative – eg. Polycythaemia Rubra Vera)
- **Pathology:**
  - **Defective Myeloblast (Myeloid Stem Cell) Differentiation → Marrow Failure → Pancytopaenia →**
    - Anaemia
    - Thrombocytopaenia → Bleeding
    - Neutropaenia → Infection
  - ***Preleukaemic - 30% May Transform to Acute Leukaemias***
- **Morphology:**
  - **Bone Marrow –** Hypercellular (Despite Pancytopaenia)
    - + Abnormal Granulocyte Precursors
    - + Abnormal Megakaryocytes
    - + Ring Sideroblasts
    - + ↑Blast Cells in BM
- **Clinical Features:**
  - **Most Common in Elderly (**60-75)
  - **Signs & Symptoms:**
    - Fatigue, Weakness, Pallor
    - Infections, Fever
    - Bruising
  - **Diagnosistic Triad:**
    - **1.** One or More Cytopaenias (Anaemia +/- Thrombocytopaenia +/- Neutropaenia)
    - **2.** Hypercellular Marrow
    - **3.** Dysmyelopoiesis in BM Precursors.
  - **Treatment:**
    - **Supportive Blood Transfusions** – RBCs & Platelets
    - **Gentle Chemotherapy**
    - **Growth Factors** – EPO (Erythropoietin) &/or G-CSF (Granulocyte Colony Stimulating Factor)
    - **Allogeneic Marrow Transplant**

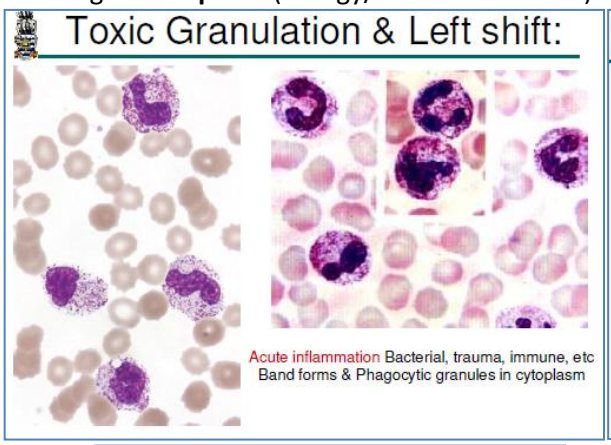


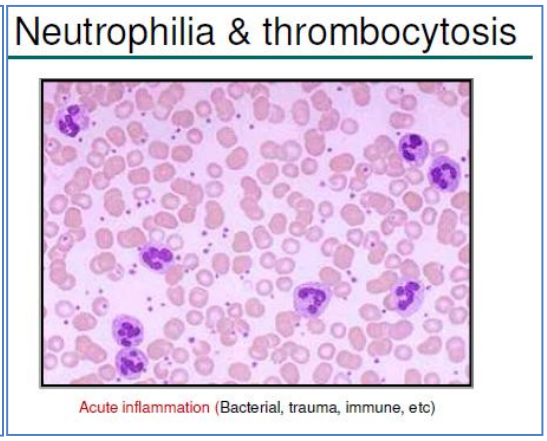
Petechiae, Purpura

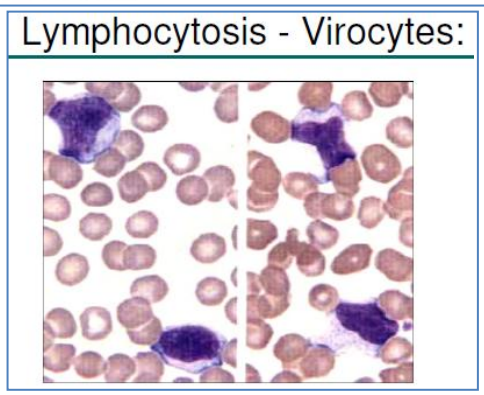
HAEMATOLOGY Pathology:
NEUTROPHILIAS & NEUTROPENIAS

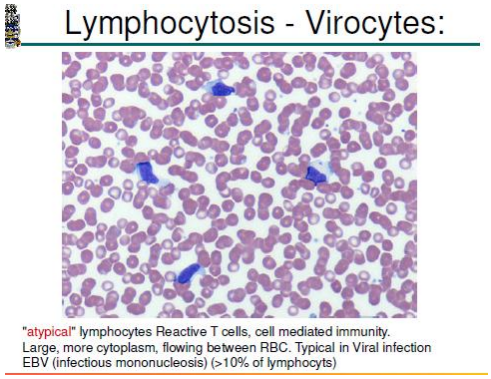
DISORDERS OF WBCS – REACTIVE *(Philias/Penias):*

- **"PHILIAS"**
  - Eg. **Neutrophilia** (Bacterial Sepsis)
  - Eg. **Lymphocytosis** (Viral Infection/Autoimmune)
  - Eg. **Eosinophilia** (Allergy/Parasite Infection)



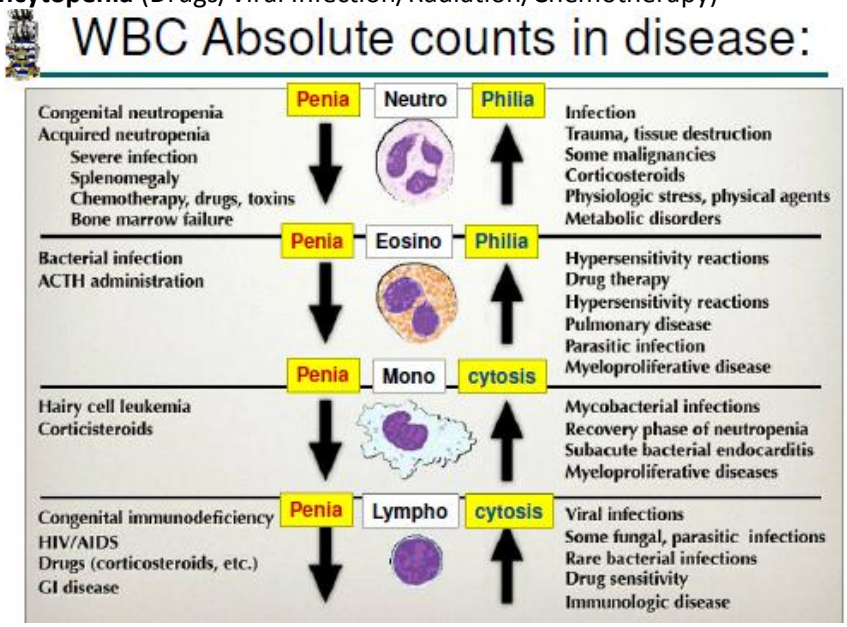






Virocytes – Reactive T-Cells. Are large, delicate cells. Typical in Viral Infection – Eg. In Infectious mononucleosis. (Reported as atypical lymphocytes on Blood Smears)

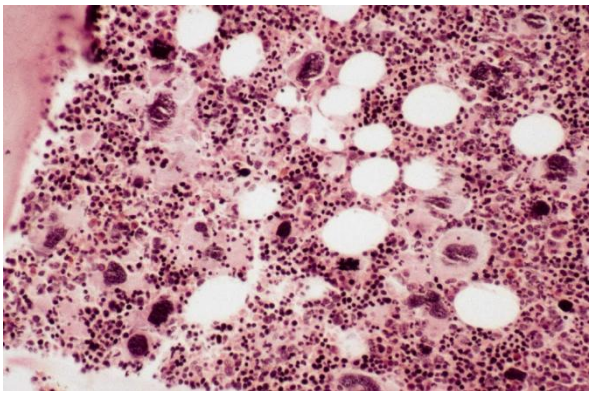
- **"PENIAS"**
  - Eg. **Neutropenia** (Drugs/Viral Infection/Radiation/Chemotherapy)
  - Eg. **Lymphopenia** (Drugs/Viral Infection/Radiation/Chemotherapy)
  - Eg. **Eosinopenia** (Drugs/Viral Infection/Radiation/Chemotherapy)
  - Eg. **Pancytopenia** (Drugs/Viral Infection/Radiation/Chemotherapy)



HAEMATOLOGY Pathology:
POLYCYTHAEMIA

POLYCYTHAEMIA/ERYTHROCYTOSIS (EXCESS RBCS):

- **Aetiology:**
  - **"True" Polycythaemia:**
    - **Primary:**
      - *Polycythaemia Vera* (Primary Proliferative Polycythaemia)
    - **Secondary:**
      - Tissue Hypoxia – Smoking (Co), High altitude, Pumonary disease, Cyanotic Heart
      - Excess EPO – Renal Diseases (Hydronephrosis/Cysts/Carcinoma)
  - **Relative "Spurious" Polycythaemia:**
    - Dehydration - Dehydration
- **Pathogenesis:**
  - **Polycythaemia Vera (Primary Proliferative Polycythaemia):**
    - (One of the Myeloproliferative Disorders [Leukaemia/Thrombocythaemia/Myelofibrosis])
    - = Malignant Proliferation of an Erythroid Progenitor cell in the Absence of EPO Stimulation.
      - → ↑↑RBC Numbers
      - (Also → ↑WBCs & Platelets → Thrombotic Complications)
  - **Excess EPO:**
    - Tissue Hypoxia → Renal Hypoxia → Stimulates EPO Secretion → ↑Erythropoiesis.
  - **Spurious Polycythaemia:**
    - Dehydration → ↓Plasma Volume → Relative ↑ in RBC Concentration.
- **Morphology:**
  - Hypercellular Marrow with Erythroid Hyperplasia
- **Clinical Features:**
  - Most common in Elderly (>60yrs)
  - May be Asymptomatic
  - **Vague Symptoms of Hyperviscosity:**
    - Headaches
    - Dizziness
    - Tinnitus
    - Visual Disturbances
  - **Pathogonomic Symptoms:**
    - Itch after a Hot Bath
    - Burning sensation in fingers & toes (AKA: Erythermalgia) – Relieved by cold.
  - **Signs:**
    - Facial Plethora
    - Splenomegaly
    - Signs of Art/Ven Thrombosis.
- **Treatment:**
  - **Treat Underlying Cause**
  - **Venesection**
  - **Anticoagulation/Antiplatelet**

Continue Reading For Bonus Supplementary Study Materials…

H

Hematology

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Acronyms

AFib	atrial fibrillation
AFLP	acute fatty liver of pregnancy
AIHA	autoimmune hemolytic anemia
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APC	activated protein C
APCR	activated protein C resistance
APS	antiphospholipid antibody syndrome
BM	bone marrow
CBC	complete blood count
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
DIC	disseminated intravascular coagulation
EPO	erythropoietin
ET	essential thrombocythemia
G6PD	glucose-6-phosphate dehydrogenase
G-CSF	granulocyte-colony stimulating factor
GSH	glutathione
HA	hemolytic anemia
Hb	hemoglobin
Hct	hematocrit
HIT	heparin-induced thrombocytopenia
HUS	hemolytic uremic syndrome
IMF	idiopathic myelofibrosis
IPC	intermittent pneumatic compression
IPSS	international prognostic scoring system
ITP	immune thrombocytopenic purpura
LMWH	low molecular weight heparin
MAHA	microangiopathic hemolytic anemia
MCH	mean corpuscular Hb
MCHC	mean corpuscular Hb concentration
MCV	mean corpuscular volume
MDS	myelodysplastic syndromes
MF	myelofibrosis
MGUS	monoclonal gammopathy of unknown significance
MM	multiple myeloma
MPN	myeloproliferative neoplasm
MPV	mean platelet volume
MUGA	multi-gated acquisition
NHL	non-Hodgkin lymphoma
PCC	prothrombin complex concentrates
Ph	Philadelphia chromosome
PNH	paroxysmal nocturnal hemoglobinuria
PV	polycythemia vera
RAEB	refractory anemia with excess blasts
RARS	refractory anemia with ringed sideroblasts
RBC	red blood cell
RCMD	refractory cytopenia with multilineage dysplasia
RCMD-RS	refractory cytopenia with multilineage dysplasia and ringed sideroblasts
RDW	RBC distribution width
SPEP	serum protein electrophoresis
sTfR	soluble transferrin receptor
TIBC	total iron binding capacity
TPO	thrombopoietin
TTP	thrombotic thrombocytopenic purpura
UFH	unfractionated heparin
UPEP	urine protein electrophoresis
VTE	venous thromboembolism
vWD	von Willebrand disease
vWF	von Willebrand factor
WBC	white blood cell
WHO	World Health Organization

Basics of Hematology

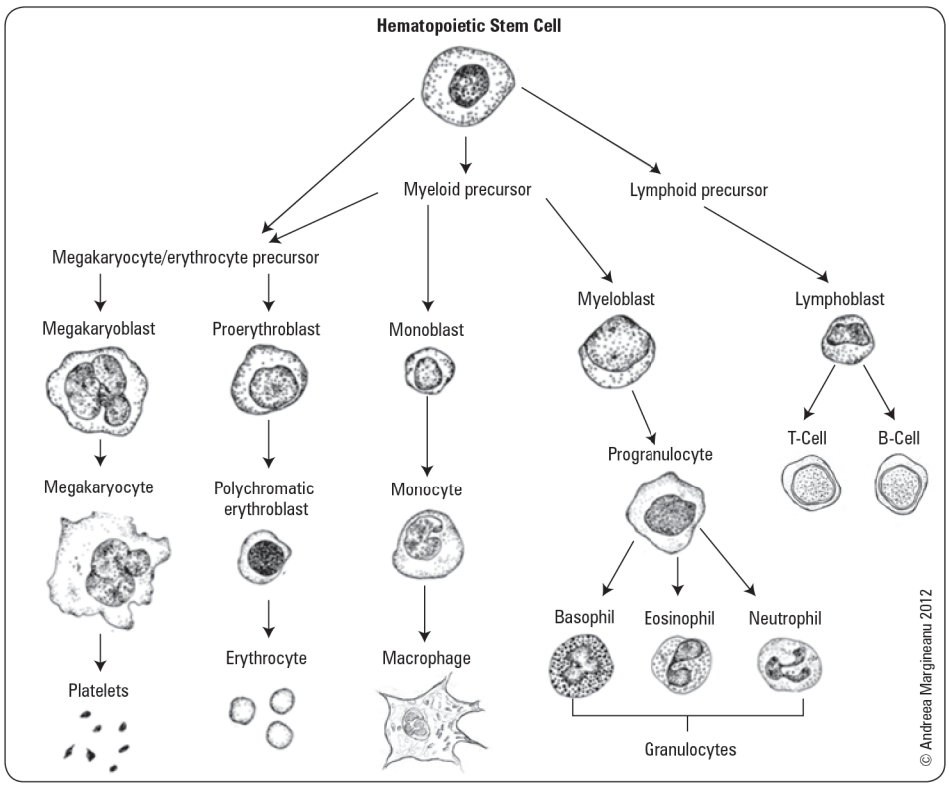


Figure 1. Hematopoiesis

Erythrocyte: carries oxygen from lungs to peripheral tissues

Reticulocyte: immature erythrocyte

Neutrophil: granulocyte integral in innate immunity; main cell in acute inflammation

Eosinophil: involved in response to parasites (especially helminths) and allergic response

Basophil: granulocyte mainly involved in allergy and parasitic infection

Lymphocyte: integral cell in adaptive immunity

Monocyte: involved in innate immunity; can differentiate into macrophage or dendritic cell

Platelet: mediator of primary hemostasis

Plasma: liquid component of blood containing water, proteins, coagulation factors, and immunoglobulins

Serum: equivalent to plasma minus clotting factors, and fibrinogen

- over 10^{11} blood cells are produced daily
- sites of hematopoiesis in adults: pelvis, sternum, vertebral bodies
- lifespan of mature cells in blood
  - erythrocytes (120 d), neutrophils (~1 d), platelets (10 d), lymphocytes (varies – memory cells persist for years)
- role of lymphoid organs
  - spleen: part of reticuloendothelial system, removes aged RBCs, removes antibody-coated bacteria/cells, site of antibody production
  - thymus: site of T-cell maturation, involutes with age
  - lymph nodes: sites of B and T-cell activation (adaptive immune response)

Complete Blood Count

Table 1. Common Terms Found on CBC

Test	Definition	Normal Values*
Red Blood Cell (RBC) Count	The number of RBCs per volume of blood	4.2-6.9 x 10^6/mm^3
Hemoglobin (Hb)	Amount of oxygen-carrying protein in the blood	130-180 g/L (male) 120-160 g/L (female)
Hematocrit (Hct)	Percentage of a given volume of whole blood occupied by packed RBCs	45%-62% (male) 37%-48% (female)
Mean Corpuscular Volume (MCV)	Measurement of size of RBCs	80-100 μm^3
Mean Corpuscular Hb (MCH)	Amount of oxygen-carrying Hb inside RBCs	27-32 pg/cell
Mean Corpuscular Hb Concentration (MCHC)	Average concentration of Hb inside RBCs	32%-36%
RBC Distribution Width (RDW)	Measurement of variance in RBC size	11.0%-15.0%
White Blood Cell (WBC) Count	The number of WBCs per volume of blood	4.3-10.8 x 10^9/mm^3
WBC Differential	Neutrophils Lymphocytes Monocytes Eosinophils Basophils	1.8-7.8 x 10^3/mm^3 0.7-4.5 x 10^3/mm^3 0.1-1.0 x 10^3/mm^3 0.0-0.4 x 10^3/mm^3 0.0-0.2 x 10^3/mm^3
Platelet Count	The number of platelets per volume of blood	150-400 x 10^9/mm^3
Mean Platelet Volume (MPV)	Measurement of platelet size	
Reticulocytes	Immature RBCs that contain no nucleus but have residual RNA	Normally make up 1% of total RBC count

*Normal values may vary depending on site and age

To estimate Hb based on the Hct, multiply by 3.3

Clinical Use of RDW
- To distinguish the etiologies of microcytosis:
  - Iron deficiency: increased RDW (anisocytosis) as cells are of varying sizes in iron deficiency
  - Thalassemia minor: normal RDW (also expect a high RBC count) as cells are of similar size due to genetic defect in Hb

Approach to Interpreting a CBC

1. consider values in the context of individual's baseline
   - up to 5% of population without disease may have values outside "normal" range
   - an individual may display a clinically significant change from their baseline without violating "normal" reference range
2. is one cell line affected or are several?
   - if all lines are low: pancytopenia (see *Pancytopenia*, H8)
   - if RBCs and platelets are low: consider a MAHA (see H22)
   - if single cell line affected: see *Common Presenting Problems*, H6

Blood Film Interpretation

RED BLOOD CELLS

Size

- microcytic (MCV <80), normocytic (MCV = 80-100), macrocytic (MCV >100)
- anisocytosis: RBCs with increased variability in size (increased RDW)
  - iron deficiency anemia, hemolytic anemias, myelofibrosis, blood transfusion, MDS

Colour

- hypochromic: increase in size of central pallor (normal = less than 1/3 of RBC diameter)
  - iron deficiency anemia, anemia of chronic disease, sideroblastic anemia
- polychromasia: increased reticulocytes (pinkish-blue cells)
  - increased RBC production by bone marrow

Shape

- poikilocytosis: increased proportion of RBCs of abnormal shape
  - iron deficiency anemia, myelofibrosis, severe B_{12} deficiency, MDS, burns

Table 2. Common Erythrocyte Shapes

Shape	Definition	Associated Conditions
Discocyte 	Biconcave disc	Normal RBC
Spherocyte 	Spherical RBC (due to loss of membrane)	Hereditary spherocytosis, immune hemolytic anemia, post-transfusion
Elliptocyte/Ovalcyte 	Oval-shaped, elongated RBCs • Elliptocytes: the RBC long axis is ≥2x the length of the short axis • Ovalcytes: the RBC long axis is <2x the length of the short axis	Hereditary elliptocytosis, megaloblastic anemia, myelofibrosis, iron-deficiency, MDS (myelodysplastic syndrome)
Schistocyte (helmet cell) 	Fragmented cells (due to traumatic disruption of membrane)	Microangiopathic hemolytic anemia (HUS/TTP, DIC, preeclampsia, HELLP, malignant HTN), vasculitis, glomerulonephritis, prosthetic heart valve
Sickle Cell 	Sickle-shaped RBC (due to polymerization of hemoglobin S)	Sickle cell disorders: HbSC, HbSS
Codocyte (target cell) 	"Bull's eye" on dried film	Liver disease, hemoglobin SC, thalassemia, Fe deficiency, asplenia
Dacrocyte (teardrop cell) 	Single pointed end, looks like a teardrop	Myelofibrosis, thalassemia major, megaloblastic anemia, bone marrow infiltration
Acanthocyte (spur cell) 	Distorted RBC with irregularly distributed thorn-like projections (due to abnormal membrane lipids)	Severe liver disease (spur cell anemia), starvation/anorexia, post-splenectomy
Echinocyte (burr cell) 	RBC with numerous regularly spaced, small spiny projections	Uremia, HUS, burns, cardiopulmonary bypass, post-transfusion, storage artifact
Rouleaux Formation 	Aggregates of RBC resembling stacks of coins (due to increased plasma concentration of high molecular weight proteins)	Pregnancy is most common cause (due to physiological increase in fibrinogen) Inflammatory conditions (due to polyclonal immunoglobulins) Plasma cell dyscrasias (due to monoclonal paraproteinemia, e.g. multiple myeloma, macroglobulinemia) Storage artifact

DIC = disseminated intravascular coagulation; HELLP = hemolysis, elevated liver enzymes, and low platelet count; HUS = hemolytic uremic syndrome; TTP = thrombotic thrombocytopenic purpura
Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012

Table 3. RBC Inclusions

Inclusions	Definition	Associated Conditions
Nucleus 	Present in erythroblasts (immature RBCs)	Hyperplastic erythropoiesis (seen in hypoxia, hemolytic anemia), BM infiltration disorders, MPNs (MF)
Heinz Bodies 	Denatured and precipitated hemoglobin	G6PD deficiency (post-exposure to oxidant), thalassemia, unstable hemoglobins
Howell-Jolly Bodies	Small nuclear remnant resembling a pyknotic nucleus	Post-splenectomy, hyposplenism (sickle cell disease), neonates, megaloblastic anemia
Basophilic Stippling 	Deep blue granulations indicating ribosome aggregation	Thalassemia, heavy metal (Pb, Zn, Ag, Hg) poisoning, megaloblastic anemia, hereditary (pyrimidine 5'nucleotidase deficiency)
Sideroblasts	Erythrocytes with Fe containing granules in the cytoplasm	Hereditary, idiopathic, drugs, hypothyroidism (see *Sideroblastic Anemia*, H16), myelodysplastic syndrome, toxins (lead)

BM = bone marrow; MF = myelofibrosis; MPN = myeloproliferative neoplasm
Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012

WHITE BLOOD CELLS

- lymphocytes: comprise 30-40% of WBCs; great variation in "normal" lymphocyte morphology
- neutrophils
  - normally only mature neutrophils (with 3-4 lobed nucleus) and band neutrophils (immediate precursor with horseshoe-shaped nucleus) are found in circulation
  - hypersegmented neutrophil: >5 lobes suggests megaloblastic process (B_{12} or folate deficiency)
  - left shift (increased granulocyte precursors)
    - seen in leukemoid reactions: acute infections, pregnancy, neonates, hypoxia, shock, myeloproliferative neoplasms (CML, MF)
- blasts
  - immature, undifferentiated precursors; associated with acute leukemia, MDS, G-CSF (growth factor that stimulates neutrophil production) use

Left Shift
Refers to an increase in granulocyte precursors in the peripheral smear (myelocytes, metamyelocytes, promyelocytes, blasts). If present, implies increased marrow production of granulocytes (e.g. inflammation, infection, G-CSF administration, CML). The presence of predominantly blasts in the peripheral smear without cells between mature neutrophil and blast suggests clonal cell disorder (MDS, acute leukemias)
This is a MEDICAL EMERGENCY

Table 4. Abnormal White Blood Cells on Film

Appearance	Definition	Associated Conditions
Reed-Sternberg Cell 	Giant, multinucleated B-lymphocyte, only seen with bone marrow specimens (classic 'owl-eye' morphology)	Primarily Hodgkin lymphoma, also seen in some non-Hodgkin lymphoma, CLL, and EBV infection
Smudge Cell 	Lymphocytes damaged during blood film preparation indicating cell fragility	CLL and other lymphoproliferative disorders Pathognomonic in EBV infection
Auer Rod 	Clumps of granular material that form long needles in the cytoplasm of myeloblasts	Pathognomonic for acute myeloid leukemia (AML)
Atypical Lymphocyte 	Pale blue cytoplasm following RBC edges with pink granules	Viruses (particularly EBV) T-cell large granular lymphocyte leukemia (T-LGL)

EBV = Epstein-Barr virus , CLL = chronic lymphocytic leukemia
Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012

PLATELETS

- small, purple, anuclear cell fragments

Bone Marrow Aspiration and Biopsy

- sites: posterior iliac crest, sternum
- analyses: most often done together
  - aspiration: takes a fluid marrow sample for cellular morphology, flow cytometry, cytogenetics, molecular studies, microbiology (C&S, acid-fast bacilli, PCR)
    - note: differential diagnosis for a "dry tap": MF, hairy cell leukemia, bone marrow infiltration
  - biopsy: takes a sample of intact bone marrow to assess histology and immunohistochemistry

Indications

- unexplained CBC abnormalities
- diagnosis and evaluation of infiltrating cancers: plasma cell disorders, leukemias, solid tumours
- diagnosis and staging of lymphoma or solid tumours
- evaluate iron metabolism and stores (gold standard, but rarely done)
- evaluate suspected deposition and storage disease (e.g. amyloidosis, Gaucher's disease)
- evaluate fever of unknown origin, suspected mycobacterial, fungal/parasitic infections, or granulomatous disease
- evaluate unexplained splenomegaly
- confirm normal bone marrow in potential allogenic hematopoietic cell donor

Contraindications

- absolute: untreated hemophilia, severe DIC, infection over skin site
- relative: recent warfarin use with INR >2.0, liver disease with associated coagulopathy
- thrombocytopenia is not a contraindication; may need platelet transfusion prior to procedure

Common Presenting Problems

Anemia

Definition

- a decrease in red blood cell (RBC) mass that can be detected by hemoglobin (Hb) concentration, hematocrit (Hct), and RBC count
  - adult males: Hb <130 g/L or Hct <0.41
  - adult females: Hb <120 g/L or Hct <0.36 (changes with pregnancy and trimester)

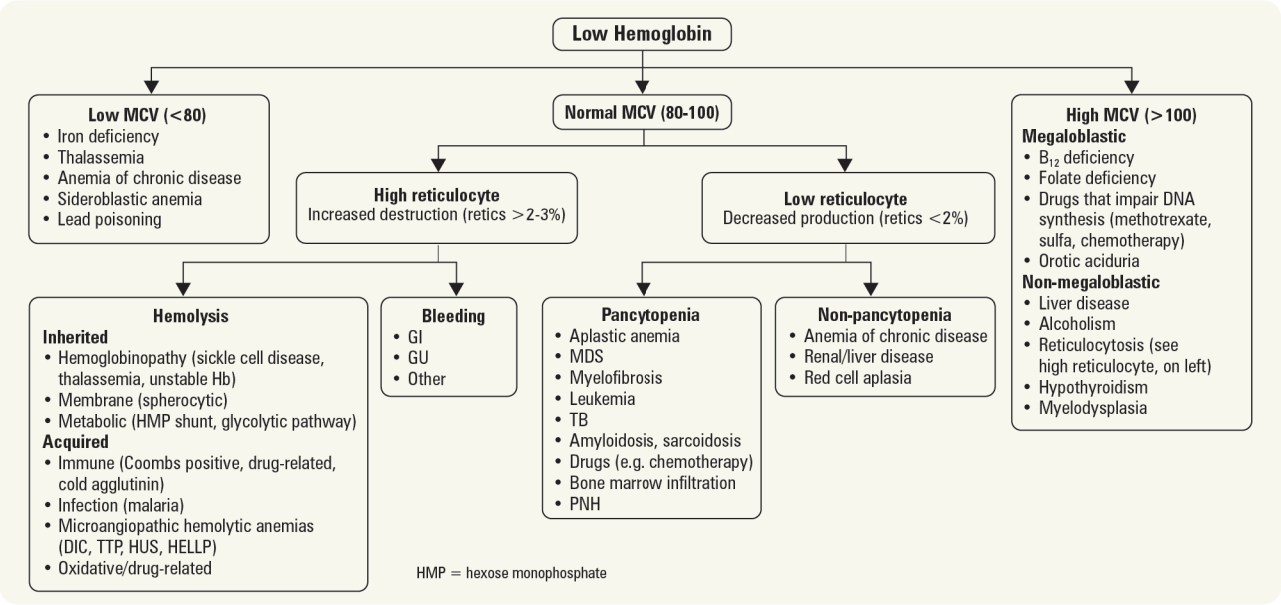


Figure 2. Approach to anemia – classification by size of RBC

Clinical Features

- history
  - symptoms of anemia (order of onset): fatigue, headache, light-headedness, malaise, weakness, decreased exercise tolerance, dyspnea, palpitations, dizziness, tinnitus, syncope
  - acute vs. chronic, bleeding, systemic illness, diet (Fe, B_{12} sources), alcohol, family history
  - menstrual history: menorrhagia, menometrorrhagia
  - rule out pancytopenia (recurrent infection, mucosal bleeding, easy bruising)
- physical signs
  - HEENT: pallor in mucous membranes and conjunctiva at Hb <90 g/L (<9 g/dL), ocular bruits at Hb <55 g/L (<5.5 g/dL), angular chelosis, jaundice
  - cardiac: tachycardia, orthostatic hypotension, systolic flow murmur, wide pulse pressure, signs of CHF
  - dermatologic: pallor in palmar skin creases at Hb <75 g/L, jaundice (if due to hemolysis), nail changes, glossitis

Reticulocytes

- Reticulocytes are immature erythrocytes and are markers of erythrocyte production
- The reticulocyte count should always be interpreted in the context of the Hb
- Should normally increase when there is a decrease in RBC
- With blood loss, reticulocytes should increase 2-3x initially and then 5-7x over the next week
- A normal reticulocyte count in anemia should be interpreted as a sign of decreased production or nutritional deficiency

Investigations

- rule out dilutional anemia (low Hb due to increased effective circulating volume)
- CBC with differential (MCV, RDW, RBC count)
- reticulocyte count – very useful to evaluate for blood cell production problems
- blood film
- rule out nutritional deficit, gastrointestinal and genitourinary disease in iron deficiency anemia
- additional laboratory investigations as indicated (see *Microcytic Anemia*, H13, *Normocytic Anemia*, H17, *Hemolytic Anemia*, H18, and *Macrocytic Anemia*, H24)

Erythrocytosis

Definition

- an increase in the number of RBCs: Hb >185 g/L or Hct >52% (males); Hb >165 or Hct >47% (females and African males)

Etiology

- relative/spurious erythrocytosis (decreased plasma volume): diuretics, severe dehydration, burns, "stress" (Gaisböck's syndrome)
- absolute erythrocytosis

Table 5. Etiology of Erythrocytosis

Primary	Secondary	Inappropriate Production of Erythropoietin
Polycythemia Vera (PV) (see *Polycythemia Vera*, H41)	**Physiologic (poor tissue oxygenation/hypoxia)** Carbon monoxide poisoning Heavy smoking High altitude **Pulmonary Disease** COPD Sleep apnea Pulmonary hypertension **Cardiovascular Disease** R to L shunt (Eisenmenger syndrome) RBC defects (Hb with increased O_2 affinity, methemoglobinemia)	**Tumours** Hepatocellular carcinoma Renal cell carcinoma Cerebellar hemangioblastoma Pheochromocytoma Uterine leiomyoma Ovarian tumour **Other** Polycystic kidney disease Post-kidney transplant Hydronephrosis Androgens Exogenous erythropoietin

Clinical Features
- secondary to high red cell mass and hyperviscosity
  - headache, dizziness, tinnitus, visual disturbances, hypertensive symptoms
  - symptoms of angina, congestive heart failure, aquagenic pruritus
- thrombosis (venous or arterial) or bleeding (abnormal platelet function)
- physical findings
  - splenomegaly ± hepatomegaly, facial plethora/ruddy complexion (70%) and/or palms, gout

Investigations
- serum erythropoietin (EPO): differentiates primary (low/normal) from other etiologies (elevated)
  - search for tumour as source of EPO as indicated (e.g. abdominal U/S, CT head)
  - JAK-2 mutation analysis: positive in >96% of cases of PV
    - only send if low/normal EPO level
- ferritin (iron deficiency can mask the diagnosis)

Treatment
- if primary: see *Polycythemia Vera*, H41
- if secondary: treat underlying cause
  - O_2 for hypoxemia, CPAP for sleep apnea, surgery for EPO-secreting tumours
  - often cardiologists will be hesitant to treat high Hct in cyanotic patients

Thrombocytopenia

Definition
- platelet count <150 x10^9/L

Clinical Features
- history: bleeding gums, epistaxis, bleeding post-surgical procedures, metromenorrhagia
- physical exam: bruising, petechiae, ecchymoses, non-palpable purpura
  - hemarthrosis and deep muscle hematomas are rarely initial signs in patients with primary hemostatic disorders
- see *Disorders of Primary Hemostasis*, H27 for complications

Investigations
- CBC and differential
- blood film
  - decreased production: other cell line abnormalities, blasts, hypersegmented PMNs, leukoerythroblastic changes
  - increased destruction: large platelets, schistocytes (seen in MAHA)
  - rule out platelet clumping
- workup for nutritional deficiencies: B_{12}, RBC folate
- PT/INR, aPTT and fibrinogen if DIC suspected
- LFTs

Treatments
- life threatening bleeding: platelet transfusion (repeat CBC 1 h post-transfusion to confirm an appropriate rise in counts)
- if secondary: treat underlying cause
- ITP: see *Immune Thrombocytopenic Purpura*, H27

Rule-of-thumb: a deficit in all cell lines suggests decreased production, sequestration, or hemodilution, a deficit in platelets and RBCs suggests non-immune destruction, and an isolated thrombocytopenia suggests an immune-mediated destruction

Must rule out factitious thrombocytopenia: platelet clumping (secondary to EDTA antibodies from collection tube). This can be seen on blood film and confirmed by repeating in a citrated sample (i.e. using a sodium citrate tube to collect blood, rather than EDTA)

In hospitalized patients, drugs and infection account for the majority of cases of thrombocytopenia

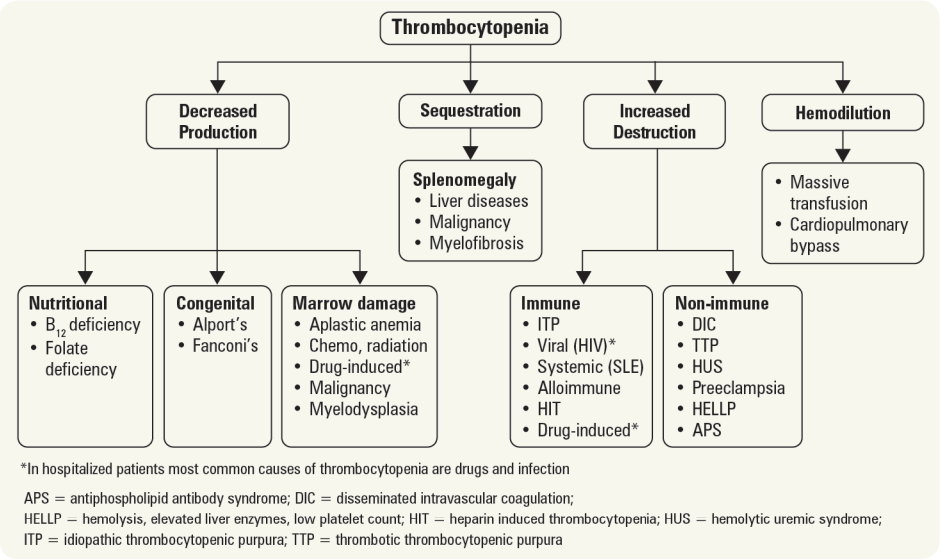


Figure 3. Approach to thrombocytopenia Adapted from: *Cecil Essentials of Medicine*

References
APS: see Hematology, H34
Aplastic Anemia: see Hematology, H17
B_{12}/Folate Deficiency: see Hematology, H24/H25
DIC: see Hematology, H32
HIT: see Hematology, H29
HIV: see Infectious Diseases, ID28
ITP: see Hematology, H27
Myelodysplasia: see Hematology, H39
Preeclampsia: see Obstetrics, OB25
SLE: see Rheumatology, RH11

Thrombocytosis

Definition
- platelet count >400 x10^9/L
- primary thrombocytosis (uncommon): due to myeloproliferative neoplasms (e.g. CML, polycythemia vera, primary myelofibrosis, essential thrombocytosis; rarely associated with MDS)
- reactive/secondary thrombocytosis (common): acute phase reactant (e.g. surgery, inflammation, infection, trauma, bleeding, iron deficiency, neoplasms, ischemic injury)

Clinical Features
- history: trauma, surgery, splenectomy, infection, inflammation, bleeding, iron deficiency, prior diagnosis of chronic hematologic disorder, constitutional symptoms (malignancy)
- vasomotor symptoms: headache, visual disturbances, lightheadedness, atypical chest pain, acral dysesthesia, erythromelalgia, livedo reticularis, aquagenic pruritus
- clotting risk, bleeding risk (rare)
- physical exam: splenomegaly can be seen in myeloproliferative neoplasms (MPNs)

Investigations
- CBC, peripheral blood film, serum ferritin concentration
- non-specific markers of infection or inflammation (e.g. CRP, ESR, ferritin)
- if reactive process has been ruled out, bone marrow biopsy may be required to rule out MPN/MDS

Treatment
- primary: ASA ± cytoreductive agents (e.g. hydroxyurea, anagrelide, interferon-α)
- secondary: treat underlying cause

Pancytopenia

Definition
- a decrease in all hematopoietic cell lines

Clinical Features
- anemia: fatigue (see *Anemia*, H6)
- leukopenia: recurrent infections (see *Neutropenia*, H9)
- thrombocytopenia: mucosal bleeding (see *Thrombocytopenia*, H7)

Investigations
- CBC, peripheral blood film, serum ferritin concentration, B_{12}, RBC folate
- non-specific markers of infection or inflammation (e.g. CRP, ESR, ferritin)
  - work up as per Figure 4 and presenting symptoms/physical exam
- if reactive process has been ruled out, bone marrow biopsy may be required to rule out MDS

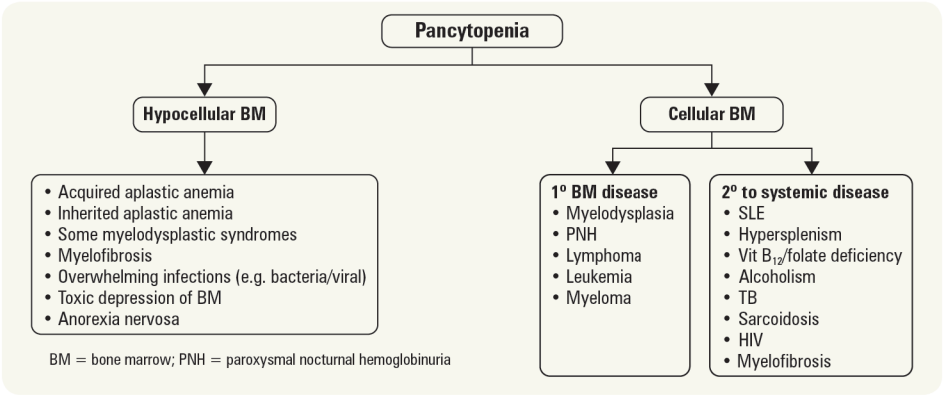


Figure 4. Approach to pancytopenia

Neutrophilia

Definition
- variable definition, but generally an absolute neutrophil count (ANC) >7.7 x 10^9/L (WHO definition)

Etiology
- primary neutrophilia
  - chronic myeloid leukemia (CML)
  - other myeloproliferative disorders: PV, ET, myelofibrosis
  - hereditary neutrophilia (autosomal dominant)
  - chronic idiopathic neutrophilia in otherwise healthy patients
  - leukocyte adhesion deficiency
- secondary neutrophilia
  - stress/exercise/epinephrine: movement of neutrophils from marginated pool into circulating pool
  - obesity
  - infection: leukocytosis with left shift ± toxic granulation, Döhle bodies (intra-cytoplasmic structures composed of agglutinated ribosomes)
  - inflammation: e.g. rheumatoid arthritis (RA), IBD, chronic hepatitis, MI, PE, burns
  - malignancy: hematologic (i.e. marrow invasion by tumour) and non-hematologic (especially large cell lung cancer)
  - medications: glucocorticoids, β-agonists, lithium, G-CSF

Clinical Features
- look for signs and symptoms of fever, inflammation, malignancy to determine appropriate further investigations
  - including lymph nodes and organomegaly
- examine oral cavity, teeth, peri-rectal area, genitals, and skin for signs of infection

Investigations
- CBC and differential: mature neutrophils or bands >20% of total WBC suggests infection/inflammation
- blood film: Döhle bodies, toxic granulation, cytoplasmic vacuoles in infection
- may require bone marrow biopsy if MPN suspected

Treatment
- directed at underlying cause

Neutropenia

Definition
- mild: ANC 1.0-1.5 x 10^9/L
- moderate: ANC 0.5-1.0 x 10^9/L (risk of infection starts to increase)
- severe: ANC <0.5 x 10^9/L
- profound: ANC <0.1 x 10^9/L for >7 d

Absolute Neutrophil Count (ANC) = WBC count x (%PMNs + %bands)

Beware of fever + ANC <0.5 x10^9/L = FEBRILE NEUTROPENIA

Etiology

Table 6. Etiology of Neutropenia

Decreased Production	Peripheral Destruction/Sequestration	Excessive Margination (Transient Neutropenia)
Infection Viral hepatitis, EBV, HIV, TB, typhoid, malaria **Hematological Diseases** Idiopathic, aplastic anemia, myelofibrosis, BM infiltration **Drug-Induced** Alkylating agents, antimetabolites, anticonvulsants, antipsychotics, anti-inflammatory agents, anti-thyroid drugs **Toxins/Chemicals** High dose radiation, benzene, DDT **Nutritional Deficiency** B_{12}, folate **Idiopathic** Constitutional neutropenia, benign cyclic neutropenia, cyclical	Anti-neutrophil antibodies Spleen or lung trapping Autoimmune disorders: RA (Felty's syndrome), SLE Granulomatosis with polyangiitis (formerly Wegener's) Drugs: haptens (e.g. α-methyldopa)	Idiopathic (most common) Overwhelming bacterial infection Hemodialysis Racial variation (e.g. African or Ashkenazi Jewish descent)

Prophylactic Hematopoietic Colony-Stimulating Factors on Mortality and Infection
Ann Intern Med 2007;147:400-411
Purpose: To review the effects of colony-stimulating factor (CSF) on mortality, infections, and febrile neutropenia in patients undergoing chemotherapy or stem-cell transplant (SCT).
Study Selection: 148 RCTs comparing the effects of CSFs to either placebo or no therapy were included. Prophylactic CSFs were given concurrently with or after initiation of chemotherapy.
Results: There were no differences in all-cause mortality or infection-related death between CSF and placebo groups. Compared to placebo or no therapy, CSFs reduced infection rate (median rate 38.9% vs. 43.1%; rate ratio 0.85), microbiologically documented infections (MR 23.5% vs. 28.6%; rate ratio 0.86), and febrile neutropenia (MR 25.3% vs. 44.2%; rate ratio 0.71).
Conclusions: Prophylactic CSFs decrease infection rates and episodes of febrile neutropenia in patients undergoing chemotherapy or SCT, but have no effect on mortality.

Clinical Features
- fever, chills (only if infection present)
- infection by endogenous bacteria (e.g. *S. aureus*, gram negatives from GI and GU tract)
- painful ulceration on skin, anus, mouth, and throat following colonization by opportunistic organisms
- avoid digital rectal exam

Investigations
- dependent on degree of neutropenia, history, and symptoms
- ranges from observation with frequent CBCs to bone marrow aspiration and biopsy

Treatment
- regular dental care: chronic gingivitis and recurrent stomatitis major sources of morbidity
- treatment of febrile neutropenia (see Infectious Diseases, ID45)
- in severe immune-mediated neutropenia, G-CSF may increase neutrophil counts
  - if no response to G-CSF, consider immunosuppression (e.g. steroids, cyclosporine, methotrexate)

G-CSF = Neupogen® = Filgrastim

Lymphocytosis

Definition
- absolute lymphocyte count >4 x 10^9/L

Etiology
- infection
  - viral infections (majority); particularly mononucleosis
  - TB, pertussis, brucellosis, toxoplasmosis
- smoking
- physiologic response to stress (e.g. trauma, status epilepticus)
- hypersensitivity (e.g. drugs, serum sickness)
- autoimmune (e.g. rheumatoid arthritis)
- neoplasm (e.g. ALL, CLL, lymphoma)

Presence of atypical lymphocytes suggests viral infection

Investigations
- peripheral smear

Presence of smudge cells suggests a lymphoproliferative disorder if persistently elevated above 5.0 x10^9/L for >3 mo; consider flow cytometry

Treatment
- treat underlying cause

Lymphopenia

Definition
- absolute lymphocyte count <1.5 x 10^9/L

Etiology
- idiopathic CD4+ lymphocytopenia
- radiation
- HIV/AIDS, hepatitis B, hepatitis C
- malignancy/chemotherapeutic agents
- malnutrition, alcoholism
- autoimmune disease (e.g. SLE)

Clinical Features
- opportunistic infections (see Infectious Diseases, ID30, ID34)

Treatment
- treat underlying cause
- treat opportunistic infections aggressively and consider antimicrobial prophylaxis (see Infectious Diseases, ID30)

Eosinophilia

Definition
- absolute eosinophil count >0.5 x 10^9/L

Etiology
- primary: due to clonal bone marrow disorder
  - if no primary etiology identified, classified as hypereosinophilic syndrome
    - 6 mo of eosinophilia with no other detectable causes
    - can involve heart, bone marrow, CNS
- secondary
  - most common causes are parasitic (usually helminth) infections and allergic reactions
  - less common causes
    - polyarteritis nodosa, see Rheumatology, RH19
    - respiratory causes (asthma, eosinophilic pneumonia, Churg-Strauss)
    - cholesterol emboli
    - hematologic malignancy: see *Chronic Myeloid Leukemia*, H40 and *Hodgkin Lymphoma*, H45
    - adrenal insufficiency, see Endocrinology, E34
    - medications (penicillins)
    - atopic dermatitis

Basophilia and/or Eosinophilia
Can be an indicator of CML or other myeloproliferative neoplasm, associated with pruritus due to excessive histamine production

Treatment
- treat underlying cause
- ensure strongyloides serology is collected to rule out infection before initiating steroids for patients at risk

Agranulocytosis

Definition
- severe depletion of granulocytes (neutrophils, eosinophils, basophils) from the blood and granulocyte precursors from bone marrow

Etiology
- associated with medications in 70% of cases: e.g. chemotherapy, clozapine, thionamides (antithyroid drugs), sulfasalazine, and ticlopidine
  - immune-mediated destruction of circulating granulocytes by drug-induced antibodies or direct toxic effects upon marrow granulocytic precursors

Clinical Features
- abrupt onset of fever, chills, weakness, and oropharyngeal ulcers

Prognosis
- high fatality without vigorous treatment

Investigations/Treatment
- discontinue offending drug
- pan-culture and screen for infection if patient is febrile (blood cultures x2, urine culture, and chest x-ray as minimum, initiate broad-spectrum antibiotics)
- consider bone marrow aspirate and biopsy if cause unclear
- consider G-CSF

Leukemoid Reactions

- blood findings resembling those seen in certain types of leukemia which reflect the response of healthy BM to cytokines released due to infection or trauma
- leukocytosis >50 x 10^9/L, marked left shift (myelocytes, metamyelocytes, bands in peripheral blood smear)

Etiology
- important to rule out CML
- differential diagnosis
  - myeloid progenitors: pneumonia, other acute bacterial infections, intoxications, burns, malignant disease, severe hemorrhage or hemolysis
  - lymphoid progenitors: pertussis, TB, infectious mononucleosis
  - monocytic progenitors: TB

Approach to Lymphadenopathy

History
- constitutional/B-symptoms: seen in TB, lymphoma, other malignancies
- growth pattern: acute vs. chronic
- exposures: cats (cat scratch – *Bartonella henselae*), ticks (Lyme disease – *Borrelia burgdorferi*), high risk behaviors (HIV)
- joint pain/swelling, rashes (connective tissue disorder)
- pruritus (seen in Hodgkin lymphoma)
- medications (can cause serum sickness → lymphadenopathy)

Constitutional/B-Symptoms
- Unexplained temperature >38°C
- Unexplained weight loss (>10% of body weight in 6 mo)
- Night sweats

Physical Exam
- basic assessment: occipital, preauricular, submandibular, cervical, supra-/infra-clavicular, axillary, epitrochlear, inguinal, popliteal nodes
  - characteristics of lymph nodes: location, size, tenderness, consistency, mobility, borders, contour
  - look for signs of infection in regions which lymph nodes drain
- determine if lymphadenopathy is localized or generalized
- localized: typically reactive or neoplastic
  - cervical (bacterial/mycobacterial infections, ENT malignancies, metastatic cancer)
  - supraclavicular
    - right (mediastinal, bronchogenic, esophageal cancer)
    - left (gastric, gall bladder, pancreas, renal, testicular/ovarian cancer)
  - axillary (cat scratch fever, breast cancer, metastatic cancer)
  - epitrochlear (infections, sarcoidosis, lymphoma)
  - lower/inguinal (STDs, skin, cervix, vulva/penis, rectum/anus cancer)
- generalized: see Table 8
- thorough examination required to assess for systemic disease

Drugs that can cause Lymphadenopathy
- Allopurinol
- Atenolol
- Captopril
- Carbamazepine
- Cephalosporins
- Gold
- Hydralazine
- Penicillin
- Phenytoin
- Primidone
- Pyrimethamine
- Quinidine
- Sulfonamides

Investigations
- CBC and differential, blood film
- ± tuberculin test, HIV RNA, VDRL, Monospot®/EBV serology, ANA, imaging as indicated
- if localized and no symptoms suggestive of malignancy, can observe 3-4 wk (if no resolution → biopsy)
- excisional biopsy is preferred as it preserves node architecture (essential for diagnosing lymphoma)
- in areas difficult to access (retroperitoneal, mediastinal/hilar) multiple core biopsies may be more practical/feasible
- FNA should NOT be used for diagnostic purposes in lymphoproliferative disease (use excisional biopsy instead)
  - helpful for recurrence of solid tumour malignancy

Table 7. Inflammatory vs. Neoplastic Lymph Nodes

Feature	Inflammatory	Neoplastic
Consistency	Rubbery	Firm/hard
Mobility	Mobile	Matted/immobile
Tenderness	Tender	Non-tender
Size	<2 cm	>2 cm

*Note: these classifications are not absolute; lymphoma and CLL nodes can feel rubbery and are frequently mobile, non-tender

Table 8. Differential Diagnosis of Generalized Lymphadenopathy

Reactive	Inflammatory	Neoplastic
Bacterial (TB, Lyme, brucellosis, cat scratch disease, syphilis)	Collagen disease (RA, dermatomyositis, SLE, vasculitis, Sjögren's)	Lymphoproliferative disorder/lymphoma
Viral (EBV, CMV, HIV)	Drug hypersensitivity	Metastatic cancer
Parasitic (toxoplasmosis)	Sarcoidosis, amyloidosis	Histiocytosis X
Fungal (histoplasmosis)	Serum sickness	

Approach to Splenomegaly

Table 9. Differential Diagnosis of Splenomegaly

Increased Demand for Splenic Function			Congestive	Infiltrative
Hematological Spherocytosis Hemoglobinopathies Hemolysis Sequestration crisis Nutritional anemias Elliptocytosis	**Infectious** CMV Bacterial endocarditis TB HIV/AIDS EBV Malaria Histoplasmosis Leishmaniasis	**Inflammatory** Felty syndrome Still's disease SLE Sarcoidosis	**Cirrhosis** Splenic vein thrombosis Portal vein obstruction Portal HTN (including right heart failure)	**Non-Malignant** Benign metaplasia Amyloidosis, Sarcoidosis Lysosomal storage diseases (Gaucher's, Niemann-Pick) Glycogen storage diseases Hamartomas Cysts Vascular abnormalities **Malignant** Leukemia (CML, CLL) Lymphoproliferative disease Hodgkin lymphoma Myeloproliferative disorders Metastatic tumour

The underlined conditions cause *massive splenomegaly* (spleen crosses midline or reaches pelvis)

Causes of Splenomegaly

CHINA
Cirrhosis/**C**ongestion (portal HTN)
Hematological
Infectious
Neoplasm (malignant, non-malignant)
Autoimmunue

Does this Adult Patient have Splenomegaly?
From The Rational Clinical Examination
JAMA 2009; http://www.jamaevidence.com/content/3487298
Study: Systematic review of articles assessing the sensitivity and specificity of clinical exam maneuvers for detecting splenomegaly.
Results: On percussion, Nixon sign had a positive likelihood ratio (+LR) of 3.6 (95% CI 1.8-7.3) and a negative likelihood ratio (–LR) of 0.41 (95% CI 0.26-0.64). Percussion of Traube's space had a +LR of 2.3 (95% CI 1.8-2.9) and –LR of 0.48 (95% CI 0.39-0.60), while Castell sign had a +LR of 1.2 (95% CI 0.98-1.6) and –LR of 0.45 (95% CI 0.19-1.1). On palpation, supine 1-handed palpation had a +LR of 8.2 (95% CI 5.8-1.2) and –LR of 0.41 (95% CI 0.30-0.57). Middleton hooking maneuver had a +LR of 6.5 (95% CI 3.1-1.5) and –LR of 0.16 (95% CI 0.08-0.32).
Conclusions: Palpation may have greater accuracy than percussion, but may be best when both are used in tandem. Specifically, Nixon sign and supine one-handed palpation are the most accurate, respectively.

History
- constitutional symptoms, feeling of fullness in LUQ
- signs or symptoms of infection or malignancy
- history of liver disease, hemolytic anemia, or high-risk exposures

Physical Exam
- jaundice, petechiae
- signs of chronic liver disease
- percussion (Castell's sign, Traube's space, Nixon's method) and palpation
- associated lymphadenopathy or hepatomegaly
- signs of CHF

Investigations
- CBC and differential, blood film
- as indicated: liver enzymes/liver function tests, reticulocyte count, Monospot®/EBV, haptoglobin, LDH, infectious, and autoimmune workup
- imaging
  - ultrasound of abdomen/liver to rule out cirrhosis and portal vein thrombosis
  - echo for cardiac function
  - CT to rule out lymphoma

Microcytic Anemia

- MCV <80 fL
- see Figure 2, *Approach to Anemia*, H6

Table 10. Iron Indices and Blood Film in Microcytic Anemia

	Lab Tests				Blood Film
	Ferritin	Serum Iron	TIBC	RDW	
Iron Deficiency Anemia	↓↓	↓	↑	↑ (>15)	• Hypochromic, microcytic
Anemia of Chronic Disease	N/↑	↓	↓	N	• Normocytic/microcytic
Sideroblastic Anemia	N/↑	↑	N	↑	• Dual population • Basophilic stippling
Thalassemia	N/↑	N/↑	N	N/↑	• Hypochromic, microcytic • Basophilic stippling • Poikilocytosis

Causes of Microcytic Anemia

TAILS
Thalassemia
Anemia of chronic disease
Iron deficiency
Lead poisoning
Sideroblastic anemia

Iron Metabolism

Iron Intake (Dietary)
- average North American adult diet = 10-20 mg iron (Fe) daily
- absorption is 5-10% (0.5-2 mg/d); enhanced by citric acid, ascorbic acid (vitamin C) and reduced by polyphenols (e.g. in tea), phytate (e.g. in bran), dietary calcium, and soy protein
- males have positive Fe balance; up to 20% of menstruating females have negative Fe balance

Iron Absorption and Transport
- dietary iron is absorbed in the duodenum (impaired by IBD, celiac disease, etc.)
- in circulation the majority of non-heme iron is bound to transferrin which transfers iron from enterocytes and storage pool sites (macrophages of the reticuloendothelial system and hepatocytes) to RBC precursors in the bone marrow

Iron Levels
- hepcidin is a hormone produced by hepatocytes that regulates systemic iron levels
  - binds to iron exporter ferroportin (on duodenal enterocytes and reticuloendothelial cells) and induces its degradation, thereby inhibiting iron export into circulation
  - hepcidin production is increased in states of inflammation (thereby mediating anemia of chronic disease) or iron overload, and decreased in states where erythropoiesis is increased (e.g. hemolysis) or oxygen tension is low

Iron Storage
- ferritin
  - ferric iron (Fe^{3+}) complexed to a protein called apoferritin (hepatocytes are main ferritin storage site)
  - small quantities are present in plasma in equilibrium with intracellular ferritin
  - also an acute phase reactant – can be spuriously elevated despite low Fe stores in response to a stressor
- hemosiderin
  - aggregates or crystals of ferritin with the apoferritin partially removed
  - macrophage-monocyte system is main source of hemosiderin storage

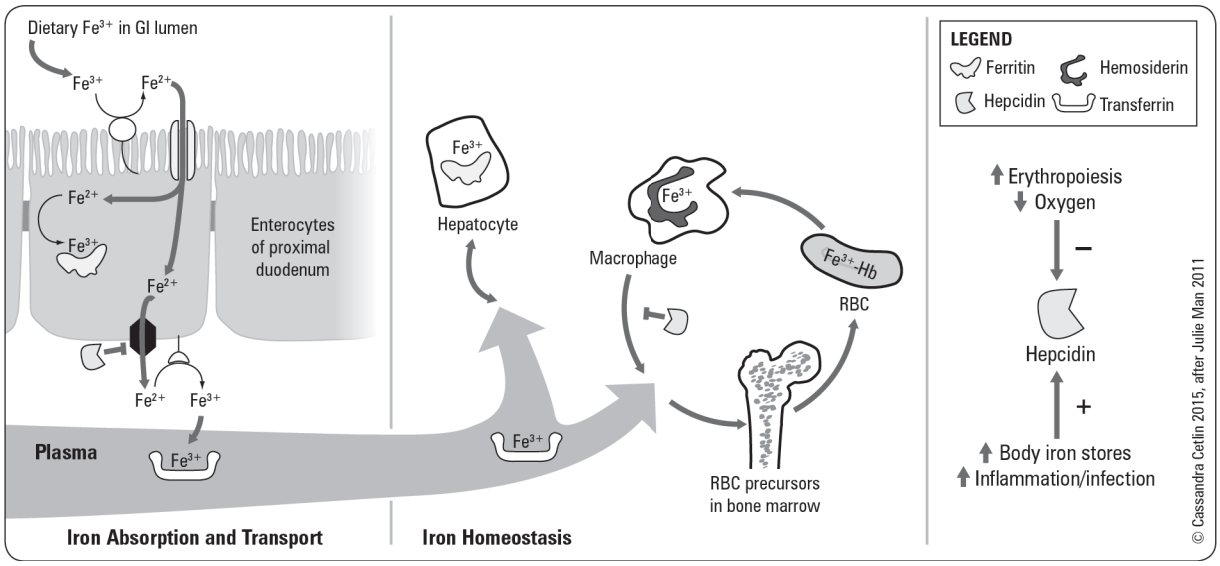


Figure 5. Iron metabolism

Iron Indices
- bone marrow aspirate: gold standard test for iron stores (rarely done)
- serum ferritin: most important blood test for iron stores
  - decreased in iron deficiency anemia
  - elevated in infection, inflammation, malignancy, liver disease, hyperthyroidism, and iron overload
- serum iron: measure of all non-heme iron present in blood
  - varies significantly daily
  - virtually all serum iron is bound to transferrin, only a trace is free or complexed in ferritin
- total iron binding capacity (TIBC): total amount of transferrin present in blood
  - normally, one third of TIBC is saturated with iron
  - high specificity for decreased iron, low sensitivity
- saturation
  - serum Fe divided by TIBC, expressed as a proportion or a percentage
  - low in iron deficiency anemia
- soluble transferrin receptor (sTfR)
  - reflects the availability of iron at the tissue level
  - the transferrin receptor is expressed on the surface of erythroblasts and is responsible for iron uptake – some is cleaved off and is present in circulation as sTfR

- in iron deficient states more transferrin receptor is expressed on erythroblasts leading to an increase in sTfR
- low in reduced erythropoiesis and iron overload
- useful in determining iron deficiency in the setting of chronic inflammatory disorders (see *Iron Deficiency Anemia*)

Iron Deficiency Anemia

- see Pediatrics, P47
- most common cause of anemia in North America

Etiology

- increased demand
  - increased physiological need for iron in the body (e.g. pregnancy)
- decreased supply: dietary deficiencies (rarely the only etiology)
  - cow's milk (infant diet)
  - "tea and toast" diet (elderly)
  - absorption imbalances
  - post-gastrectomy
  - malabsorption (IBD of duodenum, celiac disease, autoimmune atrophic gastritis)
- increased losses
  - hemorrhage
    - obvious causes: menorrhagia, abnormal uterine bleeding, frank GI bleed
    - occult: peptic ulcer disease, GI cancer
  - hemolysis
    - intravascular (e.g. PNH, cardiac valve RBC fragmentation)
    - extravascular (e.g. immune hemolytic anemias)

Clinical Features

- iron deficiency may cause fatigue before clinical anemia develops
- signs/symptoms of anemia: see *Anemia*, H6
- brittle hair, nail changes (brittle, koilonychia)
- Plummer-Vinson syndrome: dysphagia (esophageal webs), glossitis, angular stomatitis (inflammation and fissuring at the corners of the mouth)
- pica (appetite for non-food substances e.g. ice, paint, dirt)

Plummer-Vinson Syndrome Triad
- Dysphagia (esophageal)
- Glossitis
- Iron deficiency anemia

Investigations

- iron indices, including soluble transferrin receptor
  - low ferritin (<45 µg/L) is diagnostic of iron deficiency
  - ferritin is an acute phase reactant and is elevated in the setting of inflammatory conditions and liver disease; serum ferritin <100 µg/L in these settings is suggestive of iron deficiency, necessitating further workup
- peripheral blood film
  - hypochromic microcytosis: RBCs have low Hb levels due to lack of iron
  - pencil forms, anisocytosis
  - target cells (thin)
- bone marrow (gold standard but rarely done)
  - iron stain (Prussian blue) shows decreased iron in macrophages and in erythroid precursors (sideroblasts)
  - intermediate and late erythroblasts show micronormoblastic maturation

Iron deficiency anemia is a common presentation of chronic lower GI bleeds (right-sided colorectal cancer, angiodysplasia, etc.)

In males and in post-menopausal women, a GI workup is always warranted

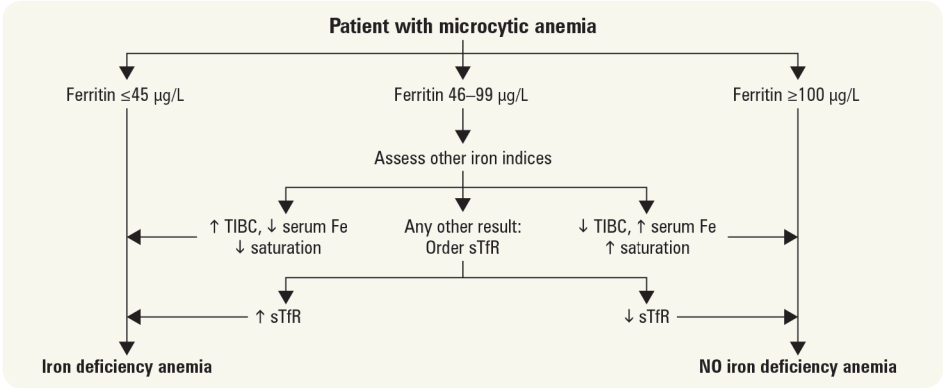


Figure 6. Approach to interpreting iron indices
Adapted from: *Am Fam Physician* 2007;75:671-678

Treatment
- treat underlying cause
- supplementation
  - oral (tablets, syrup)
    - ferrous sulphate 325 mg tid, ferrous gluconate 300 mg tid, or ferrous fumarate 300 mg tid
    - supplement until anemia corrects, then continue for 3+ mo until serum ferritin returns to normal
    - oral iron should be taken with citrus juice (vitamin C) to enhance absorption
  - IV (iron sucrose or dextran) can be used if patient cannot tolerate or absorb oral iron
- monitoring response
  - reticulocyte count will begin to increase after one wk
  - Hb normalizes by 10 g/L per wk (if no blood loss)
  - iron supplementation required for 4-6 mo to replenish stores

Anemia of Chronic Disease

Etiology
- infection, malignancy, inflammatory and rheumatologic disease, chronic renal and liver disease, endocrine disorders (e.g. DM, hypothyroidism, hypogonadism, hypopituitarism)

Pathophysiology
- an anemia of underproduction due to impaired iron utilization (hepcidin is a key regulatory peptide)
  - hepatic hepcidin production is increased in inflammatory processes, trapping iron in enterocytes and macrophages (via ferroportin inhibition) (see Figure 5)
  - reduced plasma iron levels make iron relatively unavailable for new hemoglobin synthesis
  - marrow unresponsive to normal or slightly elevated EPO
- mild hemolytic component is often present
- RBC survival is modestly decreased

Investigations
- diagnosis of exclusion
- associated with elevation in acute phase reactants (ESR, CRP, fibrinogen, platelets)
- peripheral blood
  - mild: usually normocytic and normochromic
  - moderate: may be microcytic and normochromic
  - severe: may be microcytic and hypochromic
  - absolute reticulocyte count is frequently low, reflecting overall decrease in RBC production
- "classic" serum iron indices
  - serum iron and TIBC low, % saturation normal
  - serum ferritin is normal or increased
- bone marrow
  - normal or increased iron stores
  - decreased or absent staining for iron in erythroid precursors

Iron-deficiency anemia commonly co-exists with anemia of chronic disease; suggested by:
- Serum ferritin <100 μg/L in setting of a chronic inflammatory disease
- Elevation of soluble transferrin receptor
- Absence of stainable iron on bone marrow aspiration/biopsy
- Response to a therapeutic trial of oral iron

Treatment
- treat underlying disease
- only treat anemia in patients who can benefit from a higher hemoglobin
- IV iron if no benefit from PO iron (overcomes sequestration in enterocytes)
- erythropoietin indicated in chronic renal failure; not to be used if patient has concomitant curative solid tumour malignancy; ensure Hb target <110 g/L

Sideroblastic Anemia
- uncommon compared to iron deficiency anemia or anemia of chronic disease

Sideroblasts
- erythrocytes with iron-containing (basophilic) granules in the cytoplasm
- "normal": granules are small, randomly spread in the cytoplasm
  - found in healthy individuals
- "ring": iron deposits in mitochondria, forming a ring around the nucleus
  - abnormal, large granules
  - the hallmark of sideroblastic anemia

Etiology
- due to defects in heme biosynthesis in erythroid precursors
- hereditary (rare): X-linked; median survival 10 yr
- idiopathic (acquired)
  - refractory anemia with ringed sideroblasts: a subtype of MDS (see *Myelodysplastic Syndromes*, H39)
  - may be a preleukemic phenomenon (10% transform to AML)
- reversible
  - drugs (isoniazid, chloramphenicol), alcohol, lead, copper deficiency, zinc toxicity, hypothyroidism

Clinical Features Toronto Notes 2016
- anemia symptoms (see *Anemia*, H6)
- hepatosplenomegaly, hemochromatosis

Investigations
- serum iron indices
  - increased serum Fe^{2+}, normal TIBC, increased ferritin, increased sTfR
- blood film/bone marrow biopsy
  - ringed sideroblasts (diagnostic hallmark)
  - RBCs are hypochromic; can be micro-, normo-, or macrocytic
  - anisocytosis, poikylocytosis, basophilic stippling

Treatment
- depends on etiology
  - X-linked: high dose pyridoxine (vitamin B_6) in some cases
  - acquired: EPO and G-CSF
  - reversible: remove precipitating cause
- supportive transfusions for severe anemia

Lead Poisoning

Consider lead poisoning in any child with microcytic anemia who lives in a house built before 1977

Definition/Etiology
- blood lead levels greater than 80 µg/dL, possible symptomatology at 50 µg/dL
- identify source: consider occupational history, exposures history

Clinical Features
- abdominal pain, constipation, irritability, difficulty concentrating

Treatment
- chelation therapy: dimercaprol and EDTA are first line agents

Features of Lead Poisoning

LEAD
Lead lines on gingivae and epiphyses of long bones on x-ray
Encephalopathy and **E**rythrocyte basophilic stippling
Abdominal colic and microcytic **A**nemia (sideroblastic)
Drops (wrist and foot drop)

Thalassemia

- see *Hemolytic Anemia – Thalassemia*, H19

Normocytic Anemia

- MCV 80-100 fL
- see Figure 2, *Approach to Anemia*, H6

Causes of Normocytic Anemia

ABCD
Acute blood loss
Bone marrow failure
Chronic disease
Destruction (hemolysis)

Aplastic Anemia

Definition
- destruction of hematopoietic cells of the bone marrow leading to pancytopenia and hypocellular bone marrow

Epidemiology
- occurs at any age
- slightly more common in males

Etiology

Table 11. Etiology of Aplastic Anemia

Congenital	Acquired	
Fanconi's anemia Shwachman-Diamond syndrome	**Idiopathic** Often T-cell mediated **Drugs** Dose-related (i.e. chemotherapeutics) Idiosyncratic (chloramphenicol, phenylbutazone) **Toxins** Benzene/organic solvents DDT, insectides	**Ionizing Radiation** **Post-Viral Infection** Parvovirus B19, EBV, HDV, HEV, HBV, HHV6, HIV **Autoimmune (rare)** SLE, Graft-versus-host disease **Others** PNH, pregnancy, anorexia nervosa, thymoma

Clinical Features
- can present acutely or insidiously
- symptoms of anemia (see *Anemia*, H6), thrombocytopenia (see *Thrombocytopenia*, H7), and/or infection
- ± splenomegaly and lymphadenopathy (depending on the cause)

Investigations
- exclude other causes of pancytopenia (see Figure 4), including PNH (overlap syndrome)
- CBC
  - anemia or neutropenia or thrombocytopenia (any combination) ± pancytopenia
  - decreased reticulocytes (<1% of the total RBC count)
- blood film
  - decreased number of normal RBCs
- bone marrow
  - aplasia or hypoplasia of marrow cells with fat replacement
  - decreased cellularity

Treatment
- remove offending agents
- supportive care (red cell and platelet transfusions, antibiotics)
  - judicious use so as to not increase the risk of immune sensitization to blood products
- immunosuppression (for idiopathic aplastic anemia)
  - anti-thymocyte globulin: 50-60% of patients respond
  - cyclosporine
- allogenic bone marrow transplant
- growth factors: e.g. Eltrombopag (TPO receptor agonist)

Hemolytic Anemia

- uncommon cause for anemia (<5% of cases) with many etiologies (>200)

Classification
- hereditary
  - abnormal membrane (spherocytosis, elliptocytosis)
  - abnormal enzymes (pyruvate kinase deficiency, G6PD deficiency)
  - abnormal hemoglobin synthesis (thalassemias, hemoglobinopathies)
- acquired
  - immune
    - autoimmune: warm vs. cold autoimmune hemolytic anemias (AIHA), see Table 14 *Classification of AIHA*, H22
    - alloimmune: hemolytic disease of the fetus/newborn
  - non-immune
    - MAHA: thrombus in blood vessel causes RBCs to be sheared
      - associated with DIC, HUS/TTP, preeclampsia/HELLP, vasculitides, malignant hypertension
    - other causes: PNH, hypersplenism, march hemoglobinuria (exertional hemolysis), infection (e.g. malaria), snake venoms, mechanical heart valves
- also classified as intravascular or extravascular
  - intravascular: G6PD deficiency, TTP, DIC, and PNH
  - extravascular: AIHA and membranopathies

Clinical Features Specific to HA
- jaundice
- dark urine (hemoglobinuria, bilirubin)
- cholelithiasis (pigment stones)
- potential for an aplastic crisis (i.e. BM suppression in overwhelming infection)
- iron overload with extravascular hemolysis
- iron deficiency with intravascular hemolysis

Investigations

Table 12. Investigations for Hemolytic Anemia

Screening Tests	Tests Specific For Intravascular Hemolysis
Increased LDH	Schistocytes on blood film
Decreased haptoglobin	Free hemoglobin in serum
Increased unconjugated bilirubin	Methemalbuminemia (heme + albumin)
Increased urobilinogen	Hemoglobinuria (immediate)
Reticulocytosis	Hemosiderinuria (delayed)
Tests Specific for Extravascular Hemolysis	
Direct Coombs test (direct antiglobulin test) • Detects IgG or complement on the surface of RBC • Add anti-IgG or anti-complement Ab to patient's RBCs; positive if agglutination • Indications: hemolytic disease of newborn, AIHA, hemolytic transfusion reaction	
Indirect Coombs test (indirect antiglobulin test) • Detects antibodies in serum that can recognize antigens on RBCs • Mix patient's serum + donor RBCs + Coombs serum (anti-human Ig Ab); positive if agglutination • Indications: cross-matching donor RBCs, atypical blood group, blood group Ab in pregnant women, AIHA	

On blood film schistocytes reflect an intravascular hemolysis while spherocytes usually reflect an extravascular hemolysis

Disruption of the heme breakdown pathway causes the **porphyria** disorders

Heme Breakdown

Heme
↓ Heme oxygenase
Biliverdin
↓ Biliverdin reductase
Bilirubin

Laboratory Findings in HA
- ↑ retics
- ↓ haptoglobin
- ↑ unconjugated bilirubin
- ↑ urobilinogen
- ↑ LDH

Haptoglobin is a circulating protein that mops up free hemoglobin, allowing its clearance in the spleen; when there is abundant free hemoglobin, haptoglobin is consumed, and levels decrease

Thalassemia

Definition
- defects in production of the α or β chains of hemoglobin
  - resulting imbalance in globin chains leads to ineffective erythropoiesis and hemolysis in the spleen or BM
- clinical manifestations and treatment depends on specific gene and number of alleles affected
- common features
  - increasing severity with increasing number of alleles involved
  - hypochromic microcytic anemia
  - basophilic stippling, abnormally shaped RBCs on blood film

ThalasSEAmia

β-Thal → prevalent in Mediterranean

α-Thal → prevalent in **South East Asia (SEA)** and Africa (α = Asia, Africa)

Pathophysiology
- defect may be in any of the Hb genes
  - normally 4α genes in total; 2 on each copy of chromosome 16
  - normally 2β genes in total; 1 on each copy of chromosome 11
  - fetal hemoglobin, HbF ($\alpha_2\gamma_2$), switches to adult forms HbA ($\alpha_2\beta_2$) and HbA_2 ($\alpha_2\delta_2$) at 3-6 mo of life
  - HbA constitutes 97% of adult hemoglobin
  - HbA_2 constitutes 3% of adult hemoglobin

β-Thalassemia Minor (Thalassemia Trait)

Definition
- defect in single allele of β gene (heterozygous)
- common in people of Mediterranean and Asian descent

Clinical Features
- none; a palpable spleen is very rare

Investigations
- Hb (100-140 g/L), MCV(<70), Fe (normal), RBC count (normal)
- peripheral blood film – microcytosis basophilic stippling
- Hb electrophoresis
  - specific: HbA_2 increased to 3.5-5% (normal 1.5-3.5%)
  - non-specific: 50% have slight increase in HbF

Microcytosis in β-Thal Minor

Microcytosis is much more profound and the anemia is much milder than that of iron deficiency

Treatment
- no treatment required
- genetic counselling for patient and family

β-Thalassemia Major

Definition
- defect in both alleles of β gene (homozygous, autosomal recessive)

Pathophysiology
- ineffective chain synthesis leading to ineffective erythropoiesis, hemolysis of RBCs, and increase in HbF

Clinical Features
- initial presentation at age 6-12 mo when HbA normally replaces HbF
  - severe anemia, jaundice
- iron overload progressing to hemochromatosis
  - secondary to repeated transfusions and ineffective erythropoiesis
  - leads to iron-induced organ damage (see Gastroenterology, G33)
- stunted growth and development (hypogonadal dwarf)
- gross hepatosplenomegaly (due to extramedullary hematopoiesis)
- radiologic changes (due to expanded marrow cavity) and extramedullary hematopoietic masses (erythroid tissue tumours)
  - skull x-ray has "hair-on-end" appearance
  - pathologic fractures common
- evidence of increased Hb catabolism (e.g. pigmented gallstones)
- death can result from
  - untreated anemia (should transfuse)
  - infection (should identify and treat early)
  - iron overload (common): late complication from repeated transfusions and ineffective erythropoiesis

Hemochromatosis Clinical Features

ABCDH
- arthralgia
- bronze skin
- cardiomyopathy, cirrhosis of liver
- diabetes (pancreatic damage)
- hypogonadism (anterior pituitary damage)

Investigations
- CBC: Hb 40-60 g/L (4-6 g/dL)
- Hb electrophoresis
  - HbA: 0-10% (normal >95%)
  - HbA_2 >2.5%
  - HbF: 90-100%

Treatment
- lifelong regular transfusions to suppress endogenous erythropoiesis
- iron chelation (e.g. deferoxamine, deferasirox, deferiprone) to prevent iron overload in organs and the formation of free radicals (which promote tissue damage and fibrosis)
- folic acid supplementation if not transfused
- allogenic bone marrow transplantation
- splenectomy (now performed less frequently)

β-Thalassemia Intermedia

Definition
- clinical diagnosis in patients whose clinical manifestations are too mild to be classified as thalassemia major, but too severe to be classified as thalassemia minor

Clinical Features
- wide variety of clinical phenotypes
- in most cases of TI, both β-globin genes affected
- three main mechanisms account for the milder phenotype compared to thalassemia major: (1) subnormal (vs. absent) beta-chain synthesis, (2) increased number of gamma chains, (3) coinheritance of alpha thalassemia (in some cases)
- complications more commonly seen in TI than thalassemia major include extramedullary hematopoiesis, leg ulcers, gallstones, thrombosis, and pulmonary hypertension

α-Thalassemia

Definition
- defect(s) in α genes
- similar geographic distribution as β-thalassemia, but higher frequency among Asians and Africans

Clinical Features
- 1 defective α gene (aa/a-): clinically silent; normal Hb, normal MCV
- 2 defective α genes (cis: aa/-- or trans: a-/a-): decreased MCV, normal Hb
  - N.B. cis 2-gene deletion more common in Asia vs. trans 2-gene deletion more common in Africa – this leads to increased risk of fetal hydrops in offspring of Asian patients vs. African patients
- 3 defective α genes (a-/--): HbH (β4) disease; presents in adults, decreased MCV, decreased Hb, splenomegaly
- 4 defective α genes (--/--): Hb Barts (γ4) disease (hydrops fetalis); usually incompatible with life

Investigations
- peripheral blood film – screen for HbH inclusion bodies with supravital stain
- Hb electrophoresis not diagnostic for α-thalassemia
- DNA analysis using α gene probes is the only way to confirm the diagnosis
- referral to genetic counselor prior to childbearing for patients with 2-gene cis deletion (or 3-gene deletion), due to risk of fetal hydrops if partner also carries thalassemia trait

Treatment
- depends on degree of anemia
  - 1 or 2 defective α genes: no treatment required
  - HbH disease: similar to β-thalassemia intermedia
  - HbBarts: intrauterine transfusion

Sickle Cell Disease

Definition

- sickling disorders arise due to a mutant β-globin chain, most commonly caused by a Glu → Val substitution at position 6 (chromosome 11) resulting in HbS variant, rather than HbA (normal adult Hb)
  - increased incidence of HbS allele with African or Mediterranean heritage (thought to be protective against malaria)
- sickle cell disease occurs when an individual has two HbS genes (homozygous, HbSS) or one HbS gene + another mutant β-globin gene (compound heterozygote) – most commonly HbS-β-thal and HbSC disease

Pathophysiology

- at low pO_2, deoxy HbS polymerizes leading to rigid crystal-like rods that distort membranes → 'sickles'
- the pO_2 level at which sickling occurs is related to the percentage of HbS present
  - heterozygotes (HbAS); sickling occurs at a pO_2 of 40 mmHg
  - homozygotes (HbSS); sickling occurs at a pO_2 of 80 mmHg
- sickling aggravated by acidemia, increased CO_2, increased 2,3-DPG, fever, and osmolality
- fragile sickle cells then cause injury in two main ways
  1. fragile sickle cells hemolyze (nitric oxide depletion)
  2. occlusion of small vessels (hypoxia, ischemia-reperfusion injury)

Clinical Features

- HbAS (sickle cell trait): patient will be asymptomatic except during extreme hypoxia or infection
  - increased risk of renal medullary carcinoma
- SCD-SS (HbSS)
  - chronic hemolytic anemia
  - jaundice in the first yr of life
  - retarded growth and development ± skeletal changes
  - splenomegaly in childhood; splenic atrophy in adulthood
- SCD-SS often presents with acute pain episode
  1. aplastic crises
     - toxins and infections (especially parvovirus B19) transiently suppress bone marrow
  2. splenic sequestration crises
     - usually in children; significant pooling of blood in spleen resulting in acute Hb drop and shock
     - uncommon in adults due to asplenia from repeated infarction
  3. vaso-occlusive crises (infarction)
     - may affect various organs causing ischemia-reperfusion injury (especially in back, chest, abdomen, and extremities), fever, and leukocytosis
     - can cause a stroke or a silent myocadial infarction
     - precipitated by infections, dehydration, rapid change in temperature, pregnancy, menses, and alcohol
  4. acute chest syndrome (see sidebar)
- SCD-SC (most common compound heterozygote)
  - 1:833 live births in African-Americans, common in West Africa
  - milder anemia than HbSS
  - similar complications as HbSS, although typically milder and less frequent (exception is proliferative sickle retinopathy, glomerulonephritis, and avascular necrosis)
  - spleen not always atrophic in adults

Investigations

- sickle cell prep (detects sickling of RBCs under the microscope in response to O_2 lowering agent): determines the presence of a HbS allele, but does not distinguish HbAS from HbSS
- Hb electrophoresis distinguishes HbAS, HbSS, HbSC, and other variants

Table 13. Investigations for Sickle Cell Disease

	HbAS	HbSS
CBC	Normal	Increased reticulocytes, decreased Hb, decreased Hct
Peripheral Blood	Normal; possibly a few target cells	Sickled cells
Hb Electrophoresis	HbA fraction of 0.65 (65%) HbS fraction of 0.35 (35%)	No HbA, only HbS and HbF (proportions change with age); normal amount of HbA2

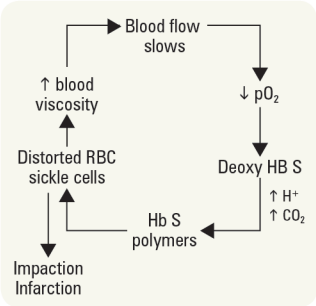


Figure 7. Pathophysiology of sickling

Functional asplenism: increased susceptibility to infection by encapsulated organisms
- *S. pneumoniae*
- *N. meningitidis*
- *H. influenza*
- *Salmonella* (osteomyelitis)

Acute Chest Syndrome
Affects 30% of patients with sickle cell disease and may be life threatening. Presentation includes dyspnea, chest pain, fever, tachypnea, leukocytosis, and pulmonary infiltrate on CXR. Caused by vaso-occlusion, infection, or pulmonary fat embolus from infarcted marrow

Organs Affected by Vaso-Occlusive Crisis

Organ	Problem
Brain	Ischemic or hemorrhagic stroke, vasculopathy
Eye	Hemorrhage, blindness
Liver	Infarcts, RUQ syndrome
Lung	Chest syndrome, long-term pulmonary hypertension
Gallbladder	Stones
Heart	Hyperdynamic flow murmurs
Spleen	Enlarged (child); atrophic (adult)
Kidney	Hematuria, loss of renal concentrating ability, proteinuria
Intestines	Acute abdomen
Placenta	Stillbirths
Penis	Priapism
Digits	Dactylitis
Femoral and Humeral Head	Avascular necrosis
Bone	Infarction, infection
Ankle	Leg ulcers

Treatment
- genetic counselling
- HbAS: no treatment required
- HbSC: treatment as per HbSS, but is dictated by symptom severity
- HbSS
  1. folic acid to prevent folate deficiency
  2. hydroxyurea to enhance production of HbF
     - mechanism of action: stops repression of Hb-γ chains and/or initiates differentiation of stem cells in which this gene is active
     - presence of HbF in the SS cells decreases polymerization and precipitation of HbS
     - N.B. hydroxyurea is cytotoxic and may cause bone marrow suppression
  3. treatment of vaso-occlusive crisis
     - oxygen
     - hydration (reduces viscosity)
     - correct acidosis
     - analgesics/opiates
     - indication for exchange transfusion: acute chest syndrome, stroke, multi-organ failure, ICU admission
     - less routinely: antimicrobials for suspected infection
  4. prevention of crises
     - establish diagnosis
     - avoid conditions that promote sickling (hypoxia, acidosis, dehydration, fever)
     - vaccination in childhood (pneumococcus, meningococcus, *H. influenza* b)
     - prophylactic penicillin (age 3 mo-5 yr)
     - good hygiene, nutrition, and social support
  5. screen for complications
     - regular blood work (CBC, reticulocytes, iron indices, BUN, LFTs, creatinine)
     - urinalysis annually (proteinuria, glomerulopathy)
     - transcranial doppler annually until 16 yr old (stroke prevention)
     - retinal examinations annually from 8 yr old (screen for retinopathy)
     - echocardiography starting at 10 yr old (screen for pulmonary hypertension)

NIH Consensus Development Conference Statement: Hydroxyurea Treatment for Sickle Cell Disease
Ann Intern Med 2008;148:932-938
Efficacy: Strong evidence for adolescents and adults and there is emerging data supporting its use in children. In the single RCT, the Hb level was higher in hydroxyurea recipients than placebo recipients after 2 yr (difference, 6 g/L), as was HbF (absolute difference, 3.2%). The median number of painful crises was 44% lower than in the placebo arm. The 12 observational studies that enrolled adults reported a relative increase in HbF of 4-20% and a relative reduction in crisis rates by 68-84%. Hospital admissions declined by 18-32%.
Effectiveness: Data is limited. It seems to be highly effective but is currently underutilized.
Short-Term Harms (within 6 mo): Dose-related leukopenia, thrombocytopenia, anemia, and decreased reticulocyte count. Others include decreased sperm production and dry skin.
Long-Term Harms: Birth defects in offspring of people receiving the drug, growth delays in children receiving the drug, and cancer in both children and adults who receive the drug.

Autoimmune Hemolytic Anemia

Table 14. Classification of AIHA

	Warm	Cold
Antibody Allotype	IgG	IgM
Agglutination Temperature	37°C	4-21°C
Direct Coombs Test (direct anti-globulin test)	Positive for IgG ± complement	Positive for complement
Etiology	Idiopathic Secondary to lymphoproliferative disorder (e.g. CLL, Hodgkin lymphoma) Secondary to autoimmune disease (e.g. SLE) Drug-induced (e.g. penicillin, quinine, methyldopa)	Idiopathic Secondary to infection (e.g. mycoplasma pneumonia, EBV) Secondary to lymphoproliferative disorder (e.g. macroglobulinemia, CLL)
Blood Film	Spherocytes	Agglutination
Management	Treat underlying cause Corticosteroids Immunosuppression Splenectomy Folic acid	Treat underlying cause Warm patient Immunosuppression Plasmapheresis Folic acid

Microangiopathic Hemolytic Anemia

Definition
- hemolytic anemia due to intravascular fragmentation of RBCs

Etiology
- see *Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome*, H30
- see *Disseminated Intravascular Coagulation*, H32
- eclampsia, HELLP syndrome, AFLP (see Obstetrics, OB25, OB26)
- malignant hypertension
- vasculitis
- malfunctioning heart valves
- metastatic carcinoma
- drugs (calcineurin inhibitors, quinine, simvastatin)
- infections (severe CMV or meningococcus)
- catastrophic antiphospholipid antibody syndrome

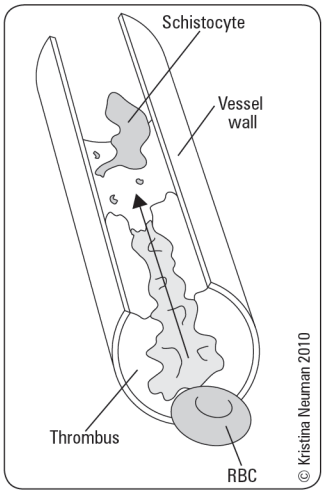


Figure 8. Schistocyte

Investigations
- blood film: evidence of hemolysis, schistocytes
- hemolytic workup
- urine: hemosiderinuria, hemoglobinuria

Hereditary Spherocytosis

- most common type of hereditary hemolytic anemia
- abnormality in RBC membrane proteins (e.g. spectrin)
  - spleen makes defective RBCs more spherocytotic (and more fragile) by membrane removal; also acts as site of RBC destruction
- autosomal dominant with variable penetrance

Investigations
- blood film (shows spherocytes), osmotic fragility (increased), molecular analysis for spectrin gene

Treatment
- in severe cases, splenectomy and vaccination against pneumococcus, meningococcus, and *H. influenza* b (avoid in early childhood)

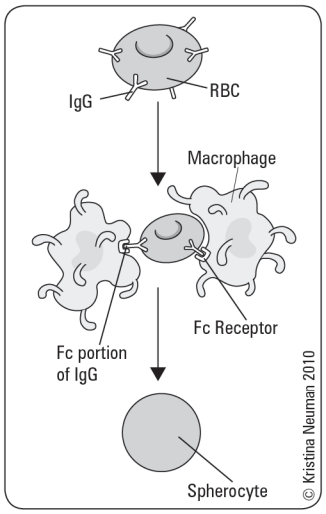


Figure 9. Spherocytosis secondary to AIHA

Hereditary Elliptocytosis

Definition/Etiology
- abnormality in spectrin interaction with other membrane proteins
- autosomal dominant
- 25-75% elliptocytes
- hemolysis is usually mild

Treatment
- immunizations; splenectomy for severe hemolysis

Glucose-6-Phosphate Dehydrogenase Deficiency

Definition
- deficiency in glucose-6-phosphate dehydrogenase (G6PD), corresponding to a lack of reduced glutathione (GSH) and leading to RBC sensitivity due to oxidative stress

Pathophysiology
- X-linked recessive, prevalent in individuals of African, Asian, and Mediterranean descent

Clinical Features
- frequently presents as episodic hemolysis precipitated by:
  - oxidative stress
  - drugs (e.g. sulfonamide, antimalarials, nitrofurantoin)
  - infection
  - food (fava beans)
- in neonates: can present as prolonged, pathologic neonatal jaundice

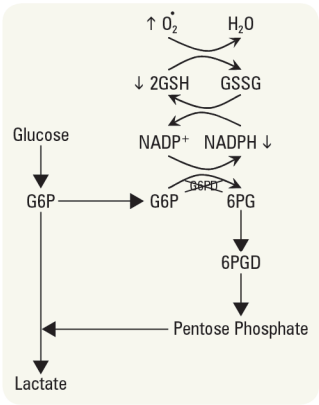


Figure 10. G6PD deficiency

Investigations
- neonatal screening
- G6PD assay (may not be useful if result is normal)
  - should not be done in acute crisis when reticulocyte count is high (reticulocytes have high G6PD levels)
- blood film
  - Heinz bodies (granules in RBCs due to oxidized Hb); passage through spleen results in the generation of bite cells
  - may have features of intravascular hemolysis (e.g. RBC fragments)

Treatment
- folic acid
- stop offending drugs and avoid triggers
- transfusion in severe cases

Macrocytic Anemia

- MCV >100 fL
- see Figure 2, *Approach to Anemia*, H6

Table 15. Comparison Between Megaloblastic and Non-Megaloblastic Macrocytic Anemia

	Megaloblastic	Non-Megaloblastic
Morphology	Large, oval, nucleated RBC precursor Hypersegmented neutrophils	Large round RBC Normal neutrophils
Pathophysiology	Failure of DNA synthesis resulting in asynchronous maturation of RBC nucleus and cytoplasm	Reflects membrane abnormality with abnormal cholesterol metabolism

Causes of Macrocytic Anemia

ABCDEF
Alcoholism (liver disease)
B$_{12}$ deficiency
Compensatory reticulocytosis
Drugs (cytotoxic, AZT)/**D**ysplasia
Endocrine (hypothyroidism)
Folate deficiency/**F**etus (pregnancy)

Characteristics of Megaloblastic Macrocytic Anemia
- Pancytopenia
- Hypersegmented neutrophils
- Megaloblastic bone marrow

Vitamin B12 Deficiency

B$_{12}$ (cobalamin) see Gastroenterology, G17 and Family Medicine – *Nutrition*, FM5
- binds to intrinsic factor (IF) secreted by gastric parietal cells
- absorbed in terminal ileum
- total body stores sufficient for 3-4 yr

Etiology

Table 16. Etiology of Vitamin B$_{12}$ Deficiency

Diet	Gastric	Intestinal Absorption	Genetic
Strict vegan More likely to present in pediatric population **Vegetarian in pregnancy**	**Mucosal atrophy** Gastritis, autoimmune **Pernicious anemia** (see below) **Post-gastrectomy**	**Malabsorption** Crohn's, celiac sprue, pancreatic insufficiency **Stagnant bowel** Blind loop, stricture **Fish tapeworm** **Resection of ileum** **Drugs** Neomycin, biguanides, PPI, N_2O anesthesia	**Transcobalamin II deficiency**

Pathophysiology of Pernicious Anemia
- auto-antibodies produced against gastric parietal cells leading to achlorhydria and lack of intrinsic factor secretion
- intrinsic factor is required to stabilize B$_{12}$ as it passes through the bowel
- decreased intrinsic factor leads to decreased ileal absorption of B$_{12}$
- may be associated with other autoimmune disorders (polyglandular endocrine insufficiency)
- F:M = 1.6:1; often >60 yr old

Clinical Features
- neurological
  - cerebral (common, reversible with B$_{12}$ therapy)
    - confusion, delirium, dementia
  - cranial nerves (rare)
    - optic atrophy
  - cord (irreversible damage)
    - subacute combined degeneration
      - posterior columns: decreased vibration sense, proprioception, and 2-point discrimination
      - pyramidal tracts: spastic weakness, hyperactive reflexes
  - peripheral neuropathy (variable reversibility)
    - usually symmetrical, affecting lower limbs more than upper limbs

Investigations
- CBC, reticulocyte count
  - anemia often severe ± neutropenia ± thrombocytopenia
  - MCV >110 fL
  - low reticulocyte count relative to the degree of anemia (<2%)
- serum B$_{12}$ and RBC folate
  - caution: low serum B$_{12}$ leads to low RBC folate because of failure of folate polyglutamate synthesis in the absence of B$_{12}$
  - alternatively, can measure elevated urine metabolites (methylmalonate, homocysteine)
- blood film
  - oval macrocytes, hypersegmented neutrophils

Oral Vitamin B$_{12}$ vs. Intramuscular Vitamin B$_{12}$ for Vitamin B$_{12}$ Deficiency
Cochrane DB Syst Rev 2005;3:CD004655
Study: Systematic review. 2 RCTs met inclusion criteria; total 108 patients with follow-up from 90 d-4 mo.
Intervention: One study evaluated 1,000 μg of oral B$_{12}$ compared to 1,000 μg IM B$_{12}$ on the same dosing schedule. The other compared 2,000 μg daily oral B$_{12}$ to 1,000 μg IM B$_{12}$ on a less frequent dosing schedule. Neurological and hematological end points were evaluated.
Results: Meta-analysis was not attempted due to study heterogeneity. Both studies reported improvements in hematological and neurological end-points in both oral and IM groups. No significant difference was observed between groups in either study.
Conclusions: Limited data suggests high dose oral vitamin B$_{12}$ (1,000-2,000 μg) is equivalent to IM vitamin B$_{12}$ on the same or less frequent dosing schedule. This data is severely limited by small sample sizes and short follow-up periods. Insufficient numbers of patients with malabsorption conditions were included to generalize these results to the entire primary care population.

- bone marrow
  - hypercellularity
  - nuclear-cytoplasmic asynchrony in RBC precursors (less mature nuclei than expected from the development of the cytoplasm)
- bilirubin and LDH
  - elevated unconjugated bilirubin and LDH due to breakdown of cells in BM
- Schilling test to distinguish pernicious anemia from other causes
  - anti-intrinsic factor antibody, anti-parietal cell antibody

Treatment
- vitamin B_{12} 1,000 µg IM monthly for life or 1,000-1,200 µg PO daily if intestinal absorption intact
- less frequent, higher doses may be as effective (e.g. 1,000 µg IM q3mo)
- watch for hypokalemia and rebound thrombocytosis when treating severe megaloblastic anemia

Schilling Test

Part 1
- Tracer dose (1 µg) of radiolabeled B_{12}, given PO
- Flushing dose (1 mg) of unlabeled B_{12} IM 1 h later to saturate tissue binders of B_{12} thus allowing radioactive B_{12} to be excreted in urine
- 24 h urine radiolabeled B_{12} measured
- Normal >5% excretion (a normal excretion will only be seen if the low B_{12} was due to dietary deficiency)

Part 2
- Same as part 1, but radiolabeled B_{12} given with oral intrinsic factor
- Should be done only if first stage shows reduced excretion
- Normal test result (>5% excretion) = pernicious anemia
- Abnormal test result (<5% excretion) = intestinal causes (malabsorption)

Folate Deficiency

- uncommon in developed countries due to extensive dietary supplementation (enriched in flour)
- folate stores are depleted in 3-6 mo
- folate commonly found in green, leafy vegetables and fortified cereals

Etiology

Table 17. Etiology of Folate Deficiency

Diet/Deficiency	Malabsorption	Drugs	Increased Demand
Alcoholism	Celiac sprue	Anti-folates (methotrexate)	Pregnancy
Substance abuse	IBD	Anticonvulsants (phenytoin)	Hemolysis
Elderly/infants	Infiltrative bowel disease	Alcohol	Prematurity
Poor intake	Short bowel syndrome	Oral contraceptive	Exfoliative dermatitis/psoriasis
			Hemodialysis

Clinical Features
- mild jaundice due to hemolysis of RBCs secondary to ineffective hemoglobin synthesis
- glossitis and angular stomatitis
- melanin pigmentation (rare)
- purpura secondary to thrombocytopenia (rare)
- unlike B_{12} deficiency, folate deficiency has no neurologic manifestations

Investigations
- similar to B_{12} deficiency (CBC, reticulocytes, blood film, RBC folate, serum B_{12})
- if decreased RBC folate, rule out B_{12} deficiency as cause

Management
- folic acid 1-5 mg PO OD x 1-4 mo; then 1 mg PO OD maintenance if cause is not reversible

Never give folate alone to an individual with megaloblastic anemia because it will mask B_{12} deficiency and neurological degeneration will continue

Hemostasis

Three Phases of Hemostasis

1. Primary Hemostasis
- goal is rapid cessation of bleeding; main effect is on mucocutaneous bleeding
- vessel injury results in collagen/subendothelial matrix exposure and release of vasoconstrictors
- blood flow is impeded and platelets come into contact with damaged vessel wall (Figure 11a)
  - adhesion: platelets adhere to subendothelium via von Willebrand factor (vWF)
  - activation: platelets are activated resulting in change of shape and release of ADP and thromboxane A_2
  - aggregation: these factors further recruit and aggregate more platelets resulting in formation of localized hemostatic plug

2. Secondary Hemostasis
- platelet plug is reinforced by production of fibrin clot (Figure 11b)
- extrinsic pathway: initiation of coagulation *in vivo*
- intrinsic pathway: amplification once coagulation has started

3. Fibrin Stabilization and Fibrinolysis (resolution)
- conversion from soluble to insoluble clot
- once healing initiated, clot dissolution (anticoagulant pathway)

Normal hemostasis occurs as a result of the balance between procoagulant and anticoagulant factors

3 Phases of Hemostasis
- Primary hemostasis
  - Vascular response and platelet plug formation via vWF
- Secondary hemostasis
  - Fibrin clot formation
- Resolution
  - Fibrinolysis

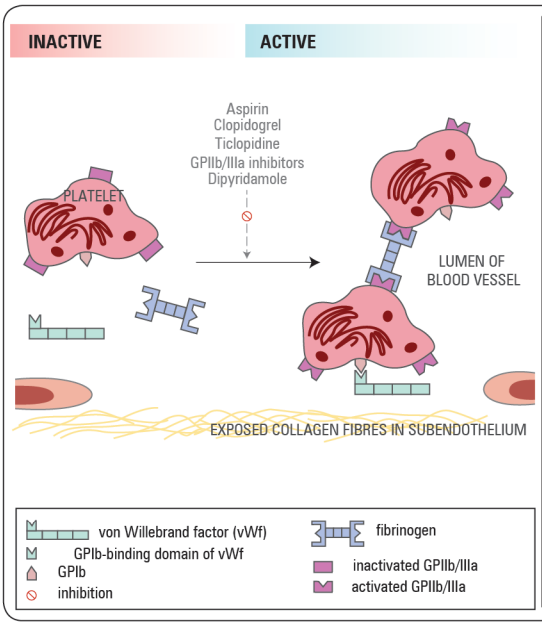


Figure 11a. Platelet activation cascade

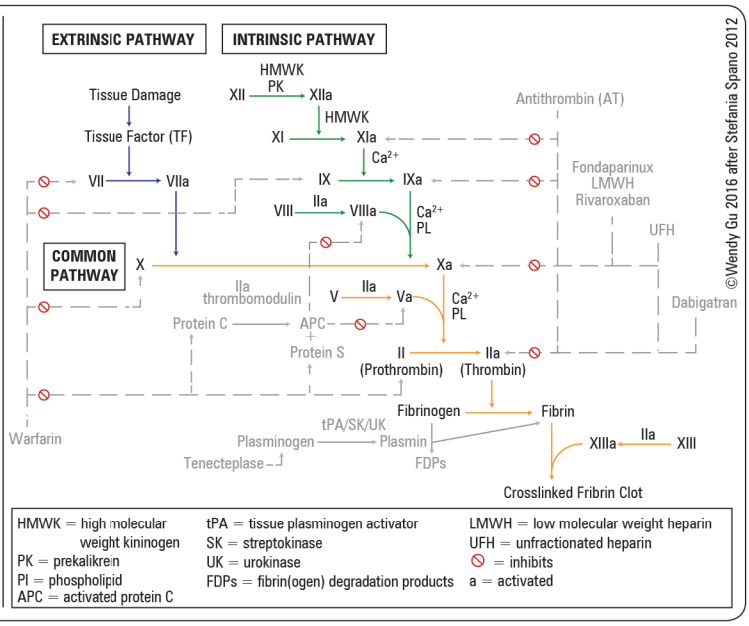


Figure 11b. Coagulation cascade

Table 18. Commonly Used Tests of Hemostasis

Type of Hemostasis	Test	Reference Range	Purpose	Examples of Associated Diagnoses
Primary	Platelet count	150-400 x 10^9/L	To quantitate platelet number	Low in ITP, HUS/TTP, DIC
Secondary	aPTT	22-35 s	Measures intrinsic pathway (factors VIII, IX, XI, XII) and common pathway Used to monitor heparin therapy and intrinsic pathway factors	Prolonged in hemophilias A and B N.B. High if antiphospholipid antibodies (i.e. lupus anti-coagulant) are present
	PT	11-24 s	Measures extrinsic pathway (factor VII in particular) and common pathway	Prolonged in factor VII deficiency
	INR	0.9-1.2	Only used to monitor warfarin therapy	
	Mixing studies		Differentiate inhibitors of clotting factor(s) from a deficiency in clotting factor(s) Mix patient's plasma with normal plasma in 1:1 ratio and repeat abnormal test	Clotting factor(s) deficiency if test becomes normal Inhibitors of clotting factor(s) if test still abnormal
Fibrinolysis	Euglobulin lysis time	N >90 min	Looks for accelerated fibrinolysis	May be accelerated in DIC or factor XIII deficiency Decreased in hereditary deficiency of fibrinogen
Other	Fibrinogen Fibrinogen degradation products (FDPs), D-dimers Specific factor assays Tests of physiological inhibitors (antithrombin, protein S, protein C, hereditary resistance to activated protein C [APC]) Tests of pathologic inhibitors (e.g. lupus anticoagulant)			

Table 19. Signs and Symptoms of Disorders of Hemostasis

	Primary (Platelet)	Secondary (Coagulation)
Surface Cuts	Excessive, prolonged bleeding	Normal/slightly prolonged bleeding
Onset After Injury	Immediate	Delayed
Site of Bleeding	Superficial i.e. mucosal (nasal, gingival, GI tract, uterine), skin	Deep i.e. joints, muscles, GI tract, GU tract Excessive post-traumatic
Lesions	Petechiae, ecchymoses	Hemarthroses, hematomas

Tests of Secondary Hemostasis

PT/INR: **T**ennis is played outside (Extrinsic pathway)

PTT: **T**able **T**ennis is played inside (Intrinsic pathway)

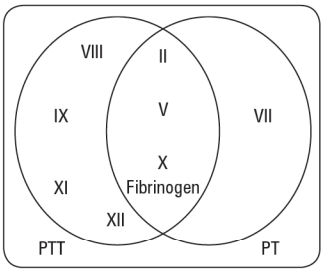


Figure 12. Clotting factors involved in PT and PTT

Causes of an Elevated PTT Without Bleeding include:

1. Factor XII deficiency
2. Lupus anti-coagulant
3. Inappropriate blood draw
4. Heparin contamination
5. Erythrocytosis (laboratory artifact)

Table 20. Lab Values in Disorders of Hemostasis

	PT	PTT	Platelet Count	RBC Count
Hemophilia A/B	N	↑	N	N
vWD	N	±	N/↓	N
DIC	↑	↑	↓	N/↓
Liver Failure	↑	N/↑	N/↓	N
ITP	N	N	↓	N
TTP	N	N	↓	↓

DIC = disseminated intravascular coagulation; ITP = idiopathic thrombocytopenic purpura; TTP = thrombotic thrombocytopenic purpura; vWD = von Willebrand disease

Disorders of Primary Hemostasis

Definition

- inability to form an adequate platelet plug due to
  - disorders of blood vessels
  - disorders of platelets: abnormal function/numbers
  - disorders of vWF

Classification

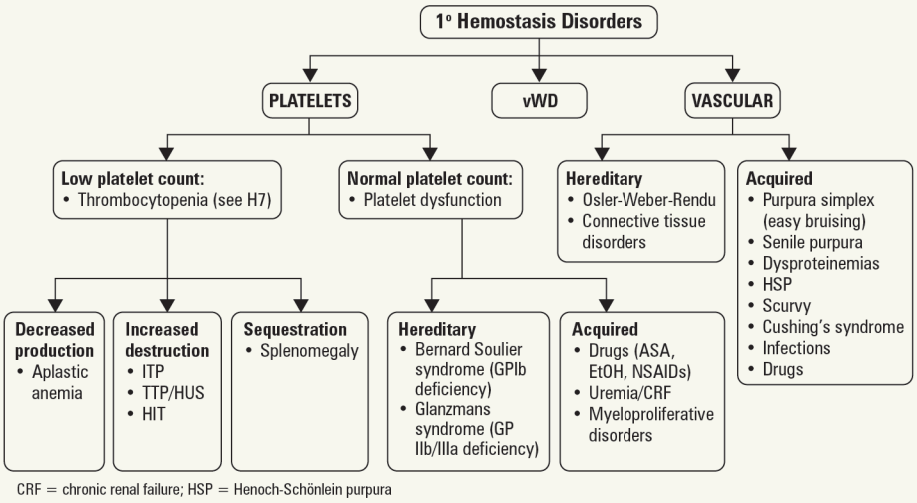


Figure 13. Approach to disorders of primary hemostasis

Drugs Associated with Thrombocytopenia

TMP-SMX	Heparin	NSAIDs
Vancomycin	Digoxin	Acetaminophen
Rifampin	Amiodarone	Ethanol
Ethambutol	Quinidine	H_2-antagonists
Amphotericin B	Quinine	

Immune Thrombocytopenic Purpura

Table 21. Immune Thrombocytopenic Purpura

Features	Acute ITP	Chronic ITP
Peak Age	2-6 yr	20-40 yr
Gender	None	F>M (3:1)
History of Recent Infection	Common	Rare
Onset of Bleed	Abrupt	Insidious
Duration	Usually wk	Months to yr
Spontaneous Remissions	80% or more	Uncommon

ACUTE (CHILD-TYPE) ITP

- see Pediatrics, P49

CHRONIC (ADULT-TYPE) ITP

- most common cause of isolated thrombocytopenia
- diagnosis of exclusion (i.e. isolated thrombocytopenia [platelets <100,000/mm^3] and the absence of any obvious initiating and/or underlying cause)

Pathophysiology
- an acquired immune-mediated disorder
  - anti-platelet antibodies bind to platelet surface → increased splenic destruction and clearance
  - impaired platelet production
  - helper T-cell and cytotoxic T-cell activation also implicated in platelet destruction

Clinical Presentation
- can present asymptomatic, with minimal bruising, or serious bleed (GI bleed, skin and mucosal hemorrhage or intracranial hemorrhage), lethargy, fatigue

Investigations
- CBC and reticulocyte count: thrombocytopenia (request retic count if not an isolated thrombocytopenia)
- PT and aPTT: normal
- peripheral blood film: decreased platelets, giant platelets (rule out platelet clumping)
- HIV, HCV serology (if risk factors are present)
- vitamin B_{12}, ANA, C3, C4, depending on clinical symptoms
- bone marrow aspirate and biopsy: increased number of megakaryocytes
  - recommended in patients >60 yr of age, pre-splenectomy or have failed multiple lines of ITP treatment, those with systemic symptoms, an abnormal blood film, and/or abnormal signs to rule out other causes of thrombocytopenia (e.g. myelodysplasia)

Mechanisms for HIV-associated Thrombocytopenia
- Direct effect of HIV on marrow
- Immune-mediated platelet destruction
- Some anti-retrovirals reduce platelet production

Treatment
- rarely indicated if platelets >30 x 10^9/L unless active bleeding, trauma, or surgery
- **emergency treatment** (active bleeding [CNS, GI, or GU] or in need of emergency surgery)
  - general measures: stop drugs reducing platelet function, control blood pressure, minimize trauma
  - corticosteroids: prednisone (1 mg/kg) or methylprednisolone (1 g/d x 3 d) or dexamethasone (40 mg PO x 4 d)
  - antifibrinolytic: tranexamic acid (1 g PO tid or 1 g IV q6h) if refractory bleeding
  - IVIg 1 g/kg/d x 2 doses, or 2 g/kg over 5 d
  - platelet transfusion: for life-threatening bleeding
  - emergency splenectomy: may be considered, vaccinations prior (pneumococcus, meningococcus, *H. influenza* b) management of intracranial bleeding: IV steroids, IVIg, platelets, emergency splenectomy, and then craniotomy; maintain Plt >100 for at least 7 wk post intracranial hemorrhage
- **non-urgent treatment** (platelet count <20-30 x 10^9/L and no bleeding OR platelet count <50 x 10^9 and significant bleeding)
  - platelet transfusion does not work
  - 1st line
    - corticosteroids (dexamethasone 40 mg/d x 4 wk or prednisone 1 mg/kg/d)
    - IVIg
    - anti-D: appropriate for Rh+ non-splenectomized patients, but can cause hemolysis (avoid if low Hb at baseline or if DAT is positive)
  - 2nd line
    - splenectomy (need vaccinations prior to splenectomy: pneumococcus, meningococcus, *H. influenza* b)
    - immunosuppressants (azathioprine, cyclophosphamide)
    - rituximab
    - danazol, vincristine
    - thrombopoietin (TPO) receptor agonists (romiplostim, eltrombopag)

Should Rituximab be Used Before or After Splenectomy in Patients with Immune Thrombocytopenic Purpura (ITP)?
Curr Opin Hematol 2007;14:642-646
Purpose: To determine whether the optimal timing for rituximab is before splenectomy, or after failure of splenectomy.
Results: Rituximab produces an initial response in approximately 60% of cases, with no significant difference between splenectomized and non-splenectomized patients. Long-term complete responses are observed in 15-20% of cases. Adverse events related to the drug were usually mild or moderate, with a low incidence of infections. Long-term safety data, however, are still lacking. Deaths have been reported for 2.9% of ITP cases treated with rituximab, but they could not be attributed to the study drug.
Conclusion: Both the response rate and the response duration appear lower following rituximab than following splenectomy. Although the side effects may be fewer, there is insufficient evidence to support the replacement of splenectomy with rituximab as a second-line treatment of chronic ITP outside a clinical trial. At the present time, the use of immunotherapy before splenectomy can be recommended only in patients at high risk for splenectomy and in those not willing to undergo surgery.

Prognosis
- ~20% will not attain a hemostatic platelet count after first and second line therapy
- fluctuating course
- overall relatively benign, mortality 1-2%
- major concern is cerebral hemorrhage at Plt <5 x 10^9/L, although very rare

Heparin-Induced Thrombocytopenia
- heparin-induced thrombocytopenia (previously known as HIT type II): immune-mediated reaction following treatment with heparin leading to coagulation activation
- heparin-associated thrombocytopenia (previously known at HIT type I): transient thrombocytopenia following administration of heparin

Table 22. Heparin-Induced Thrombocytopenia (HIT)

Pathophysiology	Immune mediated Ab recognizes a complex of heparin and platelet factor 4 (PF4) leading to platelet activation via platelet Fc receptor and activation of coagulation system
Diagnosis	50% reduction in platelets while on heparin within 5-15 wk of initiation
Onset of Decreased Platelets	5-15 wk (if previously exposed to heparin, HIT can develop in hours)
Risk of Thrombosis	~30% (25% of events are arterial)
Clinical Features	Bleeding complications uncommon Venous thrombosis: DVT, PE, limb gangrene, cerebral sinus thrombosis Arterial thrombosis: MI, stroke, acute limb ischemia, organ infarct (mesentery, kidney) Heparin-induced skin necrosis (with LMWH) Acute platelet activation syndromes: acute inflammatory reactions (e.g. fever/chills, flushing, etc.) Transient global amnesia (rare)
Specific Tests	Pre-test clinical scoring models can help rule-out HIT: 4-Ts (see Table 23) and the HIT Expert Probability (HEP) score ^{14}C serotonin release assay (uses donor platelets with ^{14}C serotonin and heparin with patient's plasma) ELISA for HIT-Ig (more sensitive, less specific than serotonin assay) Ultrasound of lower limb veins for DVT
Management	Clinical suspicion of HIT should prompt discontinuation of heparin and LWMH (specific tests take several days) Initiate anticoagulation with a non-heparin anticoagulant: e.g. argatroban, danaparoid, fondaparinaux, bivalirudin unless there is a strong contraindication (duration of treatment at least 2-3 mo if no thrombotic event, and at least 3-6 mo if thrombotic event has occurred) Warfarin should only be restarted when platelet count >100 x 10^9/L Allergy band and alert in patient records

Heparin-Associated Thrombocytopenia (previously known as HIT type I)
- Direct heparin mediated platelet aggregation (non-immune)
- Platelets >100 X 10^9/L
- Self-limited (no thrombotic risk)
- May continue with heparin therapy
- Onset 24-72 h

LMWH is also associated with HIT, but the risk is less than unfractionated heparin (2.6% in UFH vs. 0.2% in LMWH)

Table 23. The 4-T Pre-Test Clinical Scoring Model for HIT

Category	2 Points	1 Point	0 Points
1. Thrombocytopenia	Platelet count fall >50% AND platelet nadir ≥20 x 10^9/L	Platelet count fall 30-50% OR platelet nadir 10-19 x10^9/L	Platelet count fall <30% OR platelet nadir <10 x 10^9/L
2. Timing of Platelet Count Fall	Clear onset between 5-10 d of heparin exposure OR platelet count fall at ≤1 d if prior heparin exposure within last 30 d	Consistent with fall in platelet count at 5-10 d but unclear (e.g. missing platelet counts) OR onset after day 10 OR fall ≤1 d with prior heparin exposure within 30-100 d	Platelet count fall after <4 d of heparin exposure, and no recent heparin
3. Thrombosis or Other Sequelae	Confirmed new thrombosis, skin necrosis, or acute systemic reaction after IV unfractionated heparin bolus	Progressive or recurrent thrombosis, non-necrotizing (erythematous) skin lesions, or suspected thrombosis that has not been proven	None
4. Other Causes for Thrombocytopenia	None apparent	Possible	Definite

6-8 points = high probability of HIT; 4-5 points = intermediate probability of HIT; 0-3 points = low probability of HIT

J Thromb Haemos 2006;4:759-765

Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

Table 24. TTP and HUS

	TTP	HUS (See Pediatrics, P78)
Epidemiology	Predominantly adult	Predominantly children
Etiology	Deficiency of metalloproteinase that breaks down ultra-large vWF multimers • Congenital (genetic absence of ADAMTS-13) • Acquired (drugs, malignancy, transplant, HIV-associated, idiopathic)	Shiga toxin (*E. coli* serotype O157:H7) Other bacteria, viruses, genetic causes, drugs
Clinical Features	1. Thrombocytopenia 2. MAHA 3. Renal failure 4. Neurological symptoms: headache, confusion, focal defects, seizures 5. Fever	1. Severe thrombocytopenia 2. MAHA 3. Renal failure 4. Diarrhea
Investigations (both TTP, HUS)	CBC and blood film: decreased platelets and schistocytes PT, aPTT, fibrinogen: normal Markers of hemolysis: increased unconjugated bilirubin, increased LDH, decreased haptoglobin Negative Coombs test Creatinine, urea, to follow renal function Stool C&S (HUS)	
Management (both TTP, HUS)	Medical emergency Plasmapheresis ± steroids Platelet transfusion is contraindicated (increased microvascular thrombosis) Plasma infusion if plasmapheresis is not immediately available TTP mortality ~90% if untreated	

Pathophysiology of TTP
- vWF secreted by endothelial cells is a very large polymer rapidly cleaved by the ADAMTS-13 protease
- Congenital TTP is due to a deficiency in ADAMTS-13
- Antibodies against ADAMTS-13 are present in acquired TTP

Differential Diagnosis of TTP
- Sepsis
- DIC
- HELLP
- Antiphospholipid Ab syndrome
- Evans syndrome (AIHA + ITP)

von Willebrand Disease

Pathophysiology
- most common inheritable coagulation abnormality
- heterogeneous group of defects, usually mild in severity
- usually autosomal dominant (type 3 is autosomal recessive)
- qualitative or quantitative abnormality of vWF
  - vWF needed for platelet adhesion and acts as carrier for Factor VIII; abnormality of vWF can affect both primary and secondary hemostasis
  - vWF exists as a series of multimers ranging in size
    - largest multimers are most active in mediation of platelet adhesion, both large and small multimers complex with Factor VIII

Consider vWD in all women with menorrhagia

vWD is the most common inheritable couagulation abnormality

Classification
- type 1: mild quantitative defect (decreased amount of vWF and proportional decrease in vWF activity) – 75% of cases
- type 2: qualitative defect (vWF activity disproportionally lower than quantity) – 20-25% of cases
- type 3: severe total quantitative defect (no vWF produced) – rare

Clinical Features
- mild
  - asymptomatic
  - mucosal and cutaneous bleeding, easy bruising, epistaxis, menorrhagia
- moderate to severe
  - as above but more severe, occasionally soft-tissue hematomas, petechiae (rare), GI bleeding, hemarthroses

Investigations

Table 25. Investigations in vWD

Test	Expected Result	Test	Expected Result
PTT	N/↑	von Willebrand antigen	↓
Factor VIII	N/↓	Blood group	Affects antigen quantification (↓ in group O)
Plt Count	N/↓	vWF multimer analysis	Multimer variants
Ristocetin Activity	↓ (cofactor for vWF-Plt binding)		

Treatment
- desmopressin (DDAVP®) is treatment of choice for type 1 vWD
  - causes release of vWF and Factor VIII from endothelial cells
  - variable efficacy depending on disease type; tachyphylaxis occurs
  - need good response before using with further bleeding
  - caution in children due to hyponatremia
- tranexamic acid (Cyklokapron®, antifibrinolytic) to stabilize clot formation
- high-purity Factor VIII concentrate containing vWF (Hemate P®) in select cases
  - frozen plasma (FP) is not useful
  - need to monitor vWF and factor VIII levels (very high factor VIII level can cause thrombosis)
- conjugated estrogens (increase vWF levels)

Prognosis
- may fluctuate, often improves during pregnancy, inflammation, and with age

Disorders of Secondary Hemostasis

Definition
- inability to form an adequate fibrin clot
  - disorders of clotting factors or co-factors
  - disorders of proteins associated with fibrinolysis
- characterized by delayed bleeding, deep muscular bleeding, spontaneous joint bleeding

Table 26. Classification of Secondary Hemostasis Disorders

Hereditary	Acquired
Factor VIII: Hemophilia A, vWD	Liver disease
Factor IX: Hemophilia B (Christmas Disease)	DIC
Factor XI	Vitamin K deficiency
Other factor deficiencies are rare	Acquired inhibitors

Hemophilia A (Factor VIII Deficiency)

Pathophysiology
- X-linked recessive, 1/5,000 males
- mild (>5% of normal factor level), moderate (1-5%), severe (<1%)

Clinical Features
- see Table 19 – *Signs and Symptoms of Disorders of Hemostasis*, H26
- older patients may also have HIV or HCV from contaminated blood products

Investigations
- prolonged aPTT, normal INR (PT)
- decreased Factor VIII (<40% of normal)
- vWF usually normal or increased

Treatment
- desmopressin (DDAVP®) in mild hemophilia A
- recombinant Factor VIII concentrate for:
  - prophylaxis (2-3x/wk at home)
  - minor but not trivial bleeding (e.g. hemarthroses)
  - major potentially life-threatening bleeding (e.g. multiple trauma)
- anti-fibrinolytic agents (e.g. tranexamic acid)

Hemophilia A

Five Hs
Hemarthroses
Hematomas
Hematochezia
Hematuria
Head hemorrhage

Hemophilia B (Factor IX Deficiency)

- also known as Christmas disease
- X-linked recessive, 1/30,000 males
- clinical and laboratory features identical to hemophilia A (except decreased Factor IX)
- treatment: recombinant Factor IX concentrate, anti-fibrinolytic agents

Factor XI Deficiency

- also known as Rosenthal syndrome
- autosomal recessive; more common in Ashkenazi Jewish population
- usually mild, often diagnosed in adulthood
- Factor XI level does not correlate with bleeding risk
- treatment: frozen plasma, Factor XI concentrate

Liver Disease

- see Gastroenterology, G28

Pathophysiology
- deficient synthesis of all factors except VIII (also made in endothelium and in acute phase response)
- aberrant synthesis of fibrinogen
- deficient clearance of hemostatic 'debris' and fibrinolytic activators
- accelerated destruction due to dysfibrinogenemias: increased fibrinolysis, DIC
- miscellaneous: inhibition of secondary hemostasis by FDPs

Investigations
- peripheral blood film: target cells
- primary hemostasis affected
  - thrombocytopenia 2° to hypersplenism, folate deficiency, alcohol intoxication, DIC, decreased production of thrombopoietin
  - platelet dysfunction (e.g. alcohol abuse)
- secondary hemostasis affected
  - elevated INR (PT), aPTT and TT, low fibrinogen in end-stage liver disease

Investigations in Liver Disease
Factor V, VII, VIII. Expect decreased V and VII because they have the shortest half-life. Factor VIII will be normal or increased because it is produced in the endothelium

Treatment
- supportive, treat liver disease, blood products if active bleeding (frozen plasma, platelets, cryoprecipitate)

Vitamin K Deficiency

Etiology
- drugs
  - oral anticoagulants which inhibit Factors II, VII, IX, X, proteins C and S
  - antibiotics eradicating gut flora, altering vitamin K uptake
- poor diet (especially in alcoholics)
- biliary obstruction
- chronic liver disease (decreased stores)
- malabsorption (e.g. celiac disease)
- hemorrhagic disease of newborn, see Pediatrics, P68

Vitamin K Dependent Factors
Vitamin K antagonists (e.g. warfarin) affect function of these factors:
"1972 Canada vs. Soviets"
X, IX, VII, II proteins C and S

Investigations
- INR (PT) is elevated out of proportion to elevation of the aPTT
- decreased Factors II, VII, IX, X (vitamin K-dependent)

PT should improve within 24 h of vitamin K administration (onset is in 6-12 h); if not, search for other causes

Treatment
- hold anticoagulant
- vitamin K 1 mg PO for INR between 4.5-10 and no active bleeding (excludes hemorrhagic disease of the newborn)
- if bleeding, give vitamin K 10 mg IV
- if life-threatening bleeding and vitamin K antagonist used, give frozen plasma (FP) or prothrombin complex concentrate (PCC)
  - PCCs are contraindicated if there is a previous history of HIT
  - use FFP if PCC is contraindicated or unavailable
- note: excessive vitamin K will delay therapeutic warfarin anticoagulation once re-started

American Society of Hematology Choosing Wisely Recommendation
Do not administer plasma or prothrombin complex concentrates for non-emergent reversal of vitamin K antagonists (e.g. outside of the setting of major bleeding, intracranial hemorrhage, or anticipated emergent surgery)

Disseminated Intravascular Coagulation

Definition
- uncontrolled release of plasmin and thrombin leading to intravascular coagulation and depletion of platelets, coagulation factors and fibrinogen
- risk of life-threatening hemorrhage

DIC is a spectrum which may include thrombosis, bleeding, or both

Etiology
- occurs as a complication of many other conditions
- widespread endothelial damage ± extensive inflammatory cytokine release

Factor Levels in Acquired Coagulopathies

Factor	Liver Disease	Vitamin K Def	DIC
V	↓	N	↓
VII	↓	↓	↓
VIII	N/↑	N	↓

Table 27. Etiology of DIC

Activation of Procoagulant Activity	Endothelial Injury	Reticuloendothelial Injury	Vascular Stasis	Other
Antiphospholipid antibody syndrome (APS) Intravascular hemolysis Incompatible blood, malaria Tissue injury Obstetric complications, trauma, burns, crush injuries Malignancy Solid tumours, hematologic malignancies (especially APML) Snake venom, fat embolism, heat stroke	Infections/sepsis Vasculitis Metastatic adenocarcinoma Aortic aneurysm Giant hemangioma	Liver disease Splenectomy	Hypotension Hypovolemia Pulmonary embolus	Acute hypoxia/ acidosis Extracorporeal circulation

Important Etiologies of DIC

OMITS
Obstetric complications
Malignancy
Infection
Trauma
Shock

Clinical Features

- presence of both hemorrhage and clotting

Table 28. Clinical Features of DIC

Signs of Microvascular Thrombosis	Signs of Hemorrhagic Diathesis
Neurological: multifocal infarcts, delirium, coma, seizures **Skin:** focal ischemia, superficial gangrene **Renal:** oliguria, azotemia, cortical necrosis **Pulmonary:** ARDS **GI:** acute ulceration **RBC:** microangiopathic hemolysis	Bleeding from any site in the body (2º to decreased platelets and clotting factors) **Neurologic:** intracranial bleeding **Skin:** petechiae, ecchymosis, oozing from puncture sites **Renal:** hematuria **Mucosal:** gingival oozing, epistaxis, massive bleeding

Levels of fibrinogen can still be normal in DIC as it is an acute phase reactant. Serial fibrinogen levels should be measured to see if there is a trending decrease along with an increase in D-dimer

Investigations

- primary hemostasis: decreased platelets
- secondary hemostasis: prolonged INR (PT), aPTT, TT, decreased fibrinogen and other factors
- fibrinolysis: increased FDPs or D-dimers, short euglobulin lysis time (i.e. accelerated fibrinolysis)
- extent of fibrin deposition: urine output, urea, RBC fragmentation

Differential Diagnosis of Elevated D-Dimer

- Arterial thromboembolic disease (MI, CVA, acute limb ischemia, AFib, intracardiac thrombus)
- Venous thromboembolic disease (DVT, PE)
- DIC
- Preeclampsia and eclampsia
- Abnormal fibrinolysis; use of thrombolytic agents
- Cardiovascular disease, CHF
- Severe infection/sepsis/inflammation
- Surgery/trauma (tissue ischemia, necrosis)
- Systemic inflammatory response syndrome
- Vasoocclusive episode of sickle cell disease
- Severe liver disease
- Malignancy
- Renal disease (nephrotic syndrome, acute/chronic renal failure)
- Normal pregnancy
- Venous malformation

Treatment

- recognize early and treat underlying disorder
- individualized critical care support
- in hemorrhage: replacement of hemostatic elements with platelet transfusion, frozen plasma, cryoprecipitate
  - maintain platelets >50 x10^9, hemoglobin >80 g/L, calcium between 2.2-2.7 mmol/L, and avoid hypothermia
  - 4-5 units of FFP if INR >1.5 or aPTT >38
  - 10 units of cryoprecipitate if fibrinogen <1 g/L
  - 1 adult dose of buffy-coat platelets if <10 x10^9 (<20 if febrile, <50 before invasive procedure)
- in thrombotic phase: UFH or LMWH in critically ill, non-bleeding patients

Table 29. Screening Test Abnormalities in Coagulopathies

Increased INR Only	Increased PTT Only	Both Increased
Warfarin	Hemophilia A and B	Prothrombin deficiency
Vitamin K deficiency	vWD	Fibrinogen deficiency
Factor VII deficiency	Heparin	Factor V and X deficiency
Liver disease	Antiphospholipid Ab	Severe liver disease
Factor VII inhibitors	Factor inhibitors	Factor V and X, prothrombin, and fibrinogen inhibitors
	Factor XI and XII deficiency	Excessive anticoagulation

Hypercoagulable Disorders

Hypercoagulability Workup – Venous Thrombosis

- work up for malignancy is suggested in the event of abnormal blood work, constitutional symptoms or physical exam suggestive of cancer
  - all patients should have age-appropriate cancer screening if not already done
  - work up for hypercoagulable state is controversial and should only be done if it will alter treatment decisions
  - recommendations for a hypercoagulable work up include:
    - heparin resistance (ATIII deficiency)
    - warfarin-induced skin necrosis or neonatal purpura fulminans (protein C or S deficiency)
    - consider for patients with a family history of VTE who are considering OCP use
    - consider for patients who present with thrombosis at an unusual venous site
  - Arterial thrombotic events have only been proven to be associated with APLA, HIT, JAK2 MPNs, and PNH

American Society of Hematology Choosing Wisely Recommendations

1. Do not test for thrombophilia in adult patients with venous thromboembolism occurring in the setting of major transient risk factors (surgery, trauma, or prolonged immobility)
2. Do not use inferior vena cava filters routinely in patients with acute venous thromboembolism

- work up
  - initial
    - CBC, blood smear, coagulation studies, liver/renal function, urinalysis, hemolysis markers (if anemic)
    - malignancy work up (see sidebar)
    - serology: antiphospholipid antibodies (APLA): anticardiolipin antibodies (ACA), anti-β2 glycoprotein-I antibody, and lupus anticoagulant (LA)
    - activated protein C resistance (APCR)
    - DNA: FVL (Factor V Leiden), PT (prothrombin G20210A), JAK-2
    - flow cytometry: PNH work up
  - post-treatment (or ≥6 weeks, as protein levels depleted/consumed by clot)
    - antithrombin (not on heparin)
    - proteins C, S (not on warfarin)
- note: most of these tests do not change management, and a negative test does not rule out a hypercoagulable state
  - thus more focus on the reversible/treatable causes (APLA, cancer, etc.)

Common Causes of Hypercoagulability

CALM APES
Protein **C** deficiency
Antiphospholipid **A**b
Factor V **L**eiden
Malignancy
Antithrombin deficiency
Prothrombin G20210A
Increased Factor **VIII** (**E**ight)
Protein **S** deficiency

CAUSES OF HYPERCOAGULABILITY LEADING TO VENOUS THROMBOEMBOLISM

Activated Protein C Resistance (Factor V Leiden)
- most common cause of hereditary thrombophilia
- 3-7% of European Caucasian population are heterozygotes
- point mutation in the Factor V gene (R506Q) results in resistance to inactivation of Factor Va by activated protein C

Causes of Both Venous and Arterial Thrombosis include:
- Antiphospholipid antibodies
- Myeloproliferative neoplasms
- Heparin-induced thrombocytopenia
- Distal venous clot with patent foramen ovale
- Paroxysmal nocturnal hemoglobinuria

Prothrombin Gene Mutation (PT) G20210A
- 1-3% of European Caucasian population are heterozygotes
- G to A transposition at nucleotide position 20210 of the prothrombin gene promoter region results in increased levels of prothrombin, thus increased thrombin generation

Protein C and Protein S Deficiency
- protein C inactivates Factor Va and VIIIa using protein S as a cofactor
- protein C deficiency
  - homozygous or compound heterozygous: neonatal purpura fulminans
  - heterozygous
    - type I: decreased protein C levels
    - type II: decreased protein C activity
  - acquired: liver disease, sepsis, DIC, warfarin, certain chemotherapeutic agents
  - 1/3 of patients with warfarin necrosis have underlying protein C deficiency
- protein S deficiency
  - type I: decreased free and total protein S levels
  - type II: decreased protein S activity
  - type III: decreased free protein S levels
  - acquired: liver disease, DIC, pregnancy, nephrotic syndrome, inflammatory conditions, warfarin

Protein C, protein S, and ATIII are decreased during acute thrombosis – therefore to test for deficiency, must be tested outside of this time period

Antithrombin Deficiency
- antithrombin slowly inactivates thrombin in the absence of heparin, rapidly inactivates thrombin in the presence of heparin
- autosomal dominant inheritance, urinary losses in nephrotic syndrome, or reduced synthesis in liver disease
  - type I: decreased AT levels
  - type II: decreased AT activity
- diagnosis must be made outside window of acute thrombosis and anticoagulation treatment (acute thrombosis, heparin, systemic disease all decrease antithrombin levels)
- deficiency may result in resistance to unfractionated heparin (LMWH may be considered, with monitoring of anti-Xa levels)

Malignancy is a common cause of acquired hypercoagulability

Work up should include:
- Complete history and physical
- Routine blood work
- Urinalysis
- CXR
- Age appropriate screening: mammogram, Pap, PSA, colonoscopy
- Close follow-up

Additional work up may include (controversial):
- CT abdomen/pelvis

Elevated Factor VIII Levels
- an independent marker of increased incident and recurrent thrombotic risk, but levels can also be increased in numerous states as an acute phase reactant, therefore its clinical use is controversial
- genetic basis for increased levels poorly understood

Disorders of Fibrinolysis
- includes congenital plasminogen deficiency, tissue plasminogen activator deficiency, although association with VTE risk is not clear

Antiphospholipid Antibody Syndrome (APS)
- definition: ≥1 clinical and ≥1 laboratory criteria
  - clinical: thrombosis, recurrent (>3) early pregnancy losses <10 weeks, one late fetal loss ≥10 weeks (morphologically normal), or premature birth before 34 wk due to (pre)eclampsia or placental insufficiency

Although lupus anticoagulant prolongs PTT, this is a misnomer, as its main clinical feature is thrombosis

  - laboratory (must be confirmed on two occasions, tested ≥12 wks apart): anticardiolipin antibodies, anti-β2 glycoprotein-I antibody, lupus anticoagulant
- mechanism: not well understood, antibodies interact with platelet membrane phospholipid causing increased activation; can also interfere with thrombin regulation, fibrinolysis, and inhibit the protein C pathway
- see Rheumatology, RH13

Venous Thromboembolism

Definition
- thrombus formation and subsequent inflammatory response in a superficial or deep vein
- superficial thrombophlebitis, deep vein thrombosis (DVT), and pulmonary embolism (PE)
- thrombi propagate in the direction of blood flow (commonly originating in calf veins)
- more common in lower extremity than upper extremity
- incidence ~1% if age >60 yr
- most important sequelae are pulmonary embolism (~50% chance with proximal DVT) and chronic venous insufficiency

Etiology (Virchow's Triad)
- endothelial damage
  - exposes endothelium to prompt hemostasis
  - leads to decreased inhibition of coagulation and local fibrinolysis
- venous stasis
  - immobilization (post-MI, CHF, stroke, post-operative) inhibits clearance and dilution of coagulation factors
- hypercoagulability
  - inherited (see *Hypercoagulable Disorders*, H33)
  - acquired
    - age (risk increases with age)
    - surgery (especially orthopedic, thoracic, GI, and GU)
    - trauma (especially fractures of spine, pelvis, femur or tibia, spinal cord injury)
    - neoplasms (especially lung, pancreas, colon, rectum, kidney, and prostate)
    - blood dyscrasias (myeloproliferative neoplasms, especially PV, ET), PNH, hyperviscosity (multiple myeloma, polycythemia, leukemia, sickle cell disease)
    - prolonged immobilization (CHF, stroke, MI, leg injury)
    - hormone related (pregnancy, OCP, HRT, SERMs)
    - APS
    - heart failure (risk of DVT greatest with right heart failure and peripheral edema)
- idiopathic (10-20% are later found to have cancer)

Clinical Features of DVT
- absence of physical findings does not rule out disease
- unilateral leg edema, erythema, warmth, and tenderness
- palpable cord (thrombosed vein)
- phlegmasia alba dolens (white appearance) and phlegmasia cerula dolens (acute pain and edema) with massive thrombosis
- Homan's sign (pain with foot dorsiflexion) is unreliable

Differential Diagnosis of DVT
- muscle strain or tear, lymphangitis or lymph obstruction, venous valvular insufficiency, ruptured popliteal cysts, cellulitis, arterial occlusive disease

Investigations for DVT
- D-dimer test only useful to rule out DVT if negative with low clinical suspicion of disease and no other acute medical issues
- doppler ultrasound is most useful diagnostic test for DVT
  - sensitivity and specificity for proximal DVT ~95%
  - sensitivity for calf DVT ~70%
- other non-invasive tests include MRI and impedence plethysmography
- venography is the gold standard, but is expensive, invasive, and higher risk

Post-Thrombotic Syndrome
- development of chronic venous stasis signs and symptoms secondary to a deep venous thrombosis
- symptoms: pain, venous dilatation, edema, pigmentation, skin changes, venous ulcers
- clinical severity can be estimated based on the Villalta score
- large impact on quality of life following a DVT
- treatment: extremity elevation, exercise, continuous compression stockings, intermittent pneumatic compression therapy, skin/ulcer care
- for Clinical Features and Treatment of PE, see Respirology, R18

Risk of VTE in Hospitalized Patients Receiving Ineffective Antithrombotic Therapy

Risk Factor	RR (95% CI)	P-value
Age >75 yr	1.79 (1.18-2.71)	0.007
Cancer	1.58 (1.01-2.51)	
Previous VTE	1.67 (1.01-2.77)	0.08
Obesity	0.94 (0.59-1.51)	0.91
Hormone therapy	0.51 (0.08-3.38)	0.70
Heart failure	1.08 (0.72-1.62)	0.82
NYHA III	0.89 (0.55-1.43)	0.72
NYHA IV	1.48 (0.84-2.6)	0.27
Acute infectious disease	1.50 (1.00-2.26)	0.06
Acute rheumatic disease	1.45 (0.84-2.50)	0.27

Source: *JAMA* 2004;164:963-968

Virchow's Triad
- Endothelial damage
- Stasis
- Hypercoagulability

Wells' Score for DVT
Criteria (Score)
- Paralysis, paresis, or recent orthopedic casting of lower extremity (1)
- Recently bedridden (>3 d) or major surgery within past 4 wk (1)
- Localized tenderness in deep vein system (1)
- Swelling of entire leg (1)
- Calf swelling >3 cm than other leg (measured 10 cm below the tibial tuberosity) (1)
- Pitting edema greater in the symptomatic leg (1)
- Collateral non-varicose superficial veins (1)
- Active cancer or cancer treated within 6 mo (1)
- Alternative diagnosis more **likely** than DVT (e.g. Baker's cyst, cellulitis, muscle damage, superficial venous thrombosis) (-2)

Total Score Interpretation
3-8: High probability, 1-2: Moderate probability, -2-0: Low probability

Low-Molecular-Weight Heparin vs. Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer
NEJM 2003;349:146-153
Study: RCT comparing the efficacy of LMWH (dalteparin) with an oral anti-coagulant agent (coumarin) in preventing recurrent thrombosis in patients with cancer.
Methods: Patients with cancer who had acute, symptomatic proximal DVT, PE, or both were randomly assigned to either dalteparin or coumarin treatment for 6 mo.
Results: 27 of 336 patients in the dalteparin group had recurrent VTE versus 53 of 336 patients in the coumarin group (hazard ratio, 0.48; p=0.002). The probability of recurrent thromboembolism at 6 mo was 9% and 17% in dalteparin and coumarin groups respectively. There was no significant difference in bleeding rates. The mortality rate was 39% in the dalteparin group and 41% in the coumarin group.
Conclusions: In patients with cancer and acute VTE, dalteparin was more effective than coumarin in decreasing the risk of recurrent thromboembolism without increasing the risk of bleeding.

Approach to Treatment of Venous Thromboembolism

Purpose

- prevent further clot extension (3 mo duration is optimal)
- prevent acute pulmonary embolism (occurs in up to 50% of untreated patients)
- reduce the risk of recurrent thrombosis (duration depends on presence of other risk factors)
- treatment of massive ileofemoral thrombosis with acute lower limb ischemia and/or venous gangrene (phlegmasia cerulea dolens)
- limit development of late complications (e.g. postphlebitic syndrome, chronic venous insufficiency, and chronic thromboembolic pulmonary HTN)

Initial Treatment

- low molecular weight heparin (LMWH)
  - administered SC, at least as effective as UFH with a lower bleeding risk
  - advantages: predictable dose response and fixed dosing schedule; lab monitoring not required; <1% HIT; safe and effective outpatient therapy
  - disadvantages: only partially reversible by protamine, long-term use associated with osteoporosis
  - renally cleared – must adjust dose in patients with renal dysfunction
- unfractionated heparin (UFH)
  - in patient with average risk of bleed; use hospital-based nomograms that use bleeding risk and patient weight to determine appropriate dose
  - advantages: rapidly reversible by protamine
  - disadvantages: must monitor aPTT or heparin levels with adjustment of dose to reach therapeutic level (~2x normal value); monitor platelet counts for development of HIT
- alternatives to LMWH and UFH
  - direct thrombin inhibitors (hirudin, lepirudin, argatroban), Factor Xa inhibitors (fondaparinux, rivaroxaban)
  - thrombolytic drugs (e.g. streptokinase, tPA) reserved for acute limb/life-threatening thrombosis, and low bleeding risk

Long-Term Treatment

- warfarin
  - standard treatment; should be initiated with heparin overlap: dual therapy for at least 5 d, due to initial prothrombotic state, half life of vitamin K factors and risk of warfarin-induced skin necrosis
  - discontinue heparin after INR >2.0 for 2 consecutive days
  - warfarin should be dosed to maintain INR at 2-3 except in select cases
  - monitor INR twice weekly for 1-2 wk, then weekly until INR stable, then every 2-4 wk
  - LMWH more effective than warfarin at preventing recurrence of venous thrombosis in cancer patients (see sidebar, H35)
- duration of anticoagulant treatment (with warfarin unless otherwise noted)
  - first episode DVT with transient risk factor: 3 mo
  - first episode DVT with ongoing risk factor (e.g. immobility, antiphospholipid antibody) or >1 risk factor: consider indefinite therapy
  - cancer-associated DVT: prefer LMWH over warfarin for duration of cancer therapy or for as long as cancer remains active
  - first episode DVT with no identifiable risk factor (idiopathic) or single inherited risk factor (e.g. Factor V Leiden): 6-12 mo or indefinite therapy if bleeding risk low
  - recurrent DVT (2 or more episodes): indefinite therapy
- IVC filters
  - temporary filter indicated only if acute DVT (<4 wk) with significant contraindications to anticoagulant therapy (i.e. active bleeding) or if require interruption of anticoagulation (i.e. for surgery)
  - must be retrieved once safe to do so as filter is pro-thrombotic in the long-term (consider anticoagulation if not retrieved)
- special considerations
  - pregnancy: treat with LMWH during pregnancy, then LMWH or warfarin for 6 wk post-partum (minimum total anticoagulation time of 3-6 mo, but must include 6 wks post-partum, as this is a high risk period)
  - surgery: avoid elective surgery in the first month after a venous or arterial thromboembolic event
    - pre-operatively: IV heparin may be used up to 6 h pre-operatively
    - perioperatively: surgery safe when INR <1.5; warfarin should be discontinued for at least 5 d pre-operatively to allow INR to fall
    - post-operatively: IV heparin or LMWH can be used for anticoagulation (start 12 h after major surgery until therapeutic INR reached after restarting warfarin)
    - for patients at high risk for thromboembolism (VTE <12 wk, recurrent VTE, lupus anti-coagulant, atrial fibrillation with prior stroke, mechanical heart valve), IV heparin or LMWH (bridging) should be given before and after the procedure while the INR is below 2.0

Duration of Treatment with Vitamin K Antagonists in Symptomatic Venous Thromboembolism

Cochrane DB Syst Rev 2009;CD001367

Study: Meta-analysis of 8 RCTs (2,994 patients) comparing different durations of treatment with vitamin K antagonists in patients with symptomatic VTE.

Results: In patients treated with vitamin K antagonists for a prolonged period, the reduction in risk of recurrent VTE remained consistent regardless of the period of time since the index event (OR 0.18; 95%CI 0.13-0.26). In addition, there was no observed excess of VTE recurrences following cessation of prolonged treatment (i.e. rebound phenomenon) (OR 1.24; 95%CI 0.91-1.69). However, patients who received prolonged treatment had a persistent increase in their risk of major bleeding complications (OR 2.61; 95%CI 1.48-4.61).

Conclusion: Prolonged treatment with vitamin K antagonists leads to a consistent reduction in the risk of recurrent VTE for as long as therapy is continued. Therapy should be discontinued when the risk of harm from major bleeding (which remains constant over time) is of greater concern than the absolute risk of recurrent VTE (which declines over time). No specific recommendation was made regarding optimal duration of treatment.

Common Medications that Interact with Warfarin

- Acetaminophen (interference with vitamin K metabolism)
- Allopurinol
- NSAIDs (GI injury)
- Fluconazole
- Metronidazole
- Sulfamethoxazole
- Tamoxifen

Initiation of Warfarin Therapy Requires Bridging with Heparin Therapy for 4-5 Days

- 10 mg loading dose of warfarin causes a precipitous decline in protein C levels in first 36 h resulting in a transient hypercoagulable state
- Warfarin decreases Factor VII levels in first 48 h, INR is prolonged (most sensitive to Factor VII levels), however full antithrombotic effect is not achieved until Factor IX, X, and II are sufficiently reduced (occurs after ~4 d)

Low Risk Surgical Patients
<40 yr, no risk factors for VTE, general anesthetic (GA) <30 min, minor elective, abdominal, or thoracic surgery

Moderate Risk Surgical Patients
>40 yr, >1 risk factor for VTE, GA >30 min

High Risk Surgical Patients
>40 yr, surgery for malignancy or lower extremity orthopedic surgery lasting >30 min, inhibitor deficiency, or other risk factor

High Risk Medical Patients
Heart failure, severe respiratory disease, ischemic stroke and lower limb paralysis, confined to bed and have >1 additional risk factor (e.g. active cancer, previous VTE, sepsis, acute neurologic disease, IBD)

Prophylaxis
- see sidebar
- consider for those with a moderate to high risk of thrombosis without contraindications
- non-pharmacological measures include: early ambulation, elastic compression stockings (TEDs), intermittent pneumatic compression (IPC)
- UFH 5,000 IU SC bid for moderate risk
- UFH 5,000 IU SC tid or LMWH as per hospital protocol (i.e. enoxaparin 40 mg SC daily) or UFH 5,000 IU SC tid for high risk

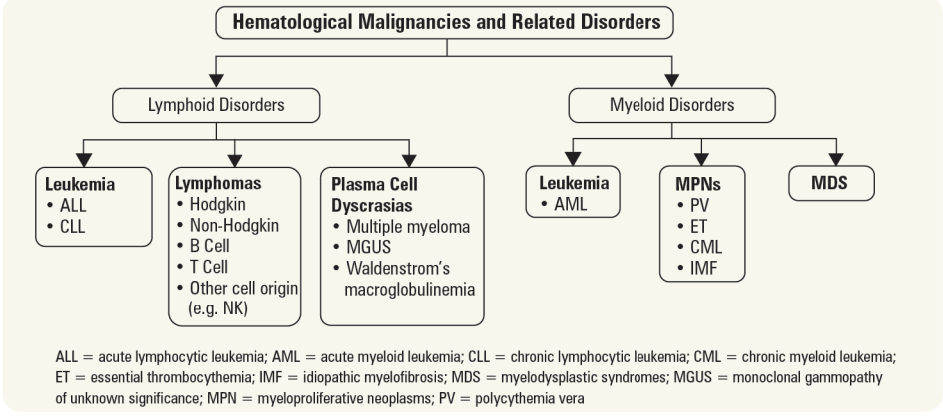
Contraindications and Adverse Reactions of Anticoagulant Therapy
- absolute: active bleeding, severe bleeding diathesis, or platelets <20 x 10^9/L (<20,000/mm^3), intracranial bleeding, neuro or ocular surgery within <10 d
- relative: mild-moderate neurologic diathesis or thrombocytopenia, brain metastases, recent major trauma, major abdominal surgery within past 2 d, GI/GU bleed within 14 d, endocarditis, severe HTN (sBP >200 or dBP >120), recent stroke

Table 30. Contraindications of Anticoagulant Therapy

Absolute Contraindications to Treatment	Relative Contraindications to Treatment
Active bleeding Severe bleeding diathesis or platelet count <20 x 10^9/L (<20,000/mm^3) Intracranial bleeding Neurosurgery or ocular surgery within 10 d	Mild-moderate bleeding diathesis or thrombocytopenia Brain metastases Recent major trauma Recent stroke Major abdominal surgery within past 2 d GI/GU bleeding within 1-4 d Endocarditis Severe hypertension (sBP >200 or dBP >120)

Treatment of Pulmonary Embolism
- see Respirology, R18

Hematologic Malignancies and Related Disorders



ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; ET = essential thrombocythemia; IMF = idiopathic myelofibrosis; MDS = myelodysplastic syndromes; MGUS = monoclonal gammopathy of unknown significance; MPN = myeloproliferative neoplasms; PV = polycythemia vera

Figure 14. Overview of hematologic malignancies and related disorders

Myeloid Malignancies

Acute Myeloid Leukemia

Definition
- rapidly progressive malignancy characterized by failure of myeloid cells to differentiate beyond blast stage

Epidemiology
- incidence increases with age; median age of onset is 65 yr old
- accounts for 10-15% of childhood leukemias

Risk Factors
- myelodysplastic syndromes (MDS), benzene, radiation, Down Syndrome, alkylating agents as treatment for previous malignancy

Typical Age of Presentation of Leukemias
- ALL: Children and older adults
- CML: 40-60 yr
- AML, CLL: >60 yr

Leukemia: malignant cells arise in bone marrow and may spread elsewhere (including blood, lymph nodes, and lymphoid tissue)

Lymphoma: malignant cells arise in lymph nodes and lymphoid tissues and may spread elsewhere (including blood and bone marrow)

BUT the location where the malignant cells are found does not solely define the type of hematologic malignancy – classified based on the characteristics of the cell (histology, histochemistry, immunophenotyping, cytogenetics, molecular changes)

Acute Leukemia
Definition (WHO): presence of 20% blast cells or greater in bone marrow at presentation

Classification: divided into myeloid (AML) and lymphoid (ALL) depending on whether blasts are myeloblasts or lymphoblasts, respectively

2008 WHO Classification of AML and Related Neoplasms
- AML with recurrent genetic abnormalities
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
- Blastic plasmacytoid dendritic cell neoplasm
- AML, not otherwise specified (equivalent FAB classification)
  - Undifferentiated (M1)
  - Myeloblastic (M2)
  - Promyelocytic (M3)
  - Myelomonocytic (M4)
  - Monocytic (M5)
  - Erythroleukemic (M6)
  - Megakaryocytic (M7)
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis

Auer rods are pathognomonic for AML

Pathophysiology
- etiology subdivided into
  - primary: *de novo*
  - secondary: hematologic malignancies (e.g. myeloproliferative disorders and MDS) or previous chemotherapeutic agents (e.g. alkylating agents)
- uncontrolled growth of blasts in marrow leads to
  - suppression of normal hematopoietic cells
  - appearance of blasts in peripheral blood
  - accumulation of blasts in other sites (e.g. skin, gums)
  - metabolic consequences; tumour lysis syndrome

Clinical Features
- anemia, thrombocytopenia (associated with DIC in promyelocytic leukemia), neutropenia (even with normal WBC), leads to infections, fever
- accumulation of blast cells in marrow
  - skeletal pain, bony tenderness (especially sternum)
- organ infiltration
  - gingival hypertrophy (particularly myelomonocytic leukemia) – may present to dentist first
  - hepatosplenomegaly (in ALL)
  - lymphadenopathy (not marked in ALL)
  - gonads (in ALL)
  - skin: leukemia cutis
  - eyes: Roth spots, cotton wool spots, vision changes (uncommon)
- leukostasis/hyperleukocytosis syndrome (medical emergency)
  - large numbers of blasts interfere with circulation and lead to hypoxia and hemorrhage – can cause diffuse pulmonary infiltrates, CNS bleeding, respiratory distress, altered mental status, priapism
  - associated with AML more than ALL
- metabolic effects; aggravated by treatment (rare)
  - increased uric acid → nephropathy, gout
  - release of phosphate → decreased Ca^{2+}, decreased Mg^{2+}
  - release of procoagulants → DIC (higher risk in acute promyelocytic leukemia)
- decreased or normal K^+ before treatment, increased K^+ after treatment (from lysed cells)

Investigations
- blood work
  - CBC: anemia, thrombocytopenia, variable WBC
  - INR, aPTT, fibrin degradation products (FDP), fibrinogen (in case of DIC)
  - increased LDH, increased uric acid, increased PO_4^{3-} (released by leukemic blasts), decreased Ca^{2+}, decreased K^+
  - baseline renal and liver function tests
- peripheral blood film – circulating blasts with Auer rods (azurophilic granules) are pathognomonic for AML
- bone marrow aspirate
  - blast count: AML >20% (normal is <5%)
  - morphologic, cytochemical, and/or immunotypic features are used to establish lineage and maturation (see sidebar for WHO classification of AML, H37)
- CXR to rule out pneumonia, ECG, MUGA scan prior to chemotherapy (cardiotoxic)

Treatment
- mainstay of treatment is chemotherapy (rapidly fatal without treatment)
  - all AML subtypes are treated similarly, except acute promyelocytic leukemia (APL) with t(15:17) translocation
    - all-trans-retinoic acid (ATRA) added to induce differentiation; arsenic trioxide + ATRA combination therapy for APL is non-inferior to traditional chemotherapy
- treatment strategy
  1. **Induction:** chemotherapy to induce complete remission of AML (see sidebar)
     - several possible regimens (e.g. cytarabine with anthracycline [daunorubicin])
     - patients with poor response to initial induction therapy – worse prognosis
     - must ensure reversal of DIC, platelet transfusions if <10
  2. **Consolidation:** to prevent recurrence
     - intensive consolidation chemotherapy
     - stem cell transplantation – autologous or allogeneic (younger patients with better performance status)
- consider acceleration with hematopoietic growth factors (e.g. G-CSF) if severe infection develops
- supportive care
  - screening for infection via regular C&S of urine, stool, sputum, oropharynx, catheter sites, perianal area
  - fever: C&S of all orifices, CXR, start antibiotics
  - platelet and RBC transfusions (irradiated to prevent transfusion-related GVHD) ± EPO
  - prevention and treatment of metabolic abnormalities
    - allopurinol, rasburicase for prevention of hyperuricemia

Cure: survival that parallels age-matched population

Complete Remission: tumour load below threshold of detectable disease (normal peripheral blood film, normal bone marrow with <5% blasts, normal clinical state)

Prognosis
- achievement of first remission
  - 70-80% if ≤60 yr old, 50% if >60 yr old median survival 12-24 mo
  - 5 yr survival 40%
  - prognosis is most related to cytogenetics; classified as favourable, intermediate, or adverse

Myelodysplastic Syndromes

Definition
- heterogeneous group of malignant stem cell disorders characterized by dysplastic and ineffective blood cell production resulting in peripheral cytopenias
- syndromes defined according to World Health Organization (WHO) classifications

2008 WHO MDS Classification
- Refractory cytopenia with unilineage dysplasia
  - Refractory anemia
  - Refractory neutropenia
  - Refractory thrombocytopenia
- Refractory anemia with ringed sideroblasts (RARS)
- Refractory cytopenia with multilineage dysplasia (RCMD)
- Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)
- Refractory anemia with excess blasts (RAEB)
- Myelodysplasic syndrome with isolated del (5q)
- Myelodysplasia unclassified (seen in cases of megakaryocyte dysplasia with fibrosis and others)
- Childhood myelodysplastic syndrome

Pathophysiology
- disordered maturation: ineffective hematopoiesis despite presence of adequate numbers of progenitor cells in bone marrow (usually hypercellular)
- intramedullary apoptosis: programmed cell death within bone marrow
  - both processes lead to reduced mature cells in periphery
- <30% develop AML

Risk Factors
- elderly, post-chemotherapy, benzene or radiation exposure
- occurs in 4/100,000 patients >60 yr old

Clinical Features
- insidious onset: associated with pancytopenia
- infections and bleeding out of proportion with peripheral blood counts

Investigations
- diagnosed by
  - anemia ± thrombocytopenia ± neutropenia
  - CBC and peripheral blood film
  - RBC: usually macrocytic with oval shaped red cells (macro-ovalocytes), decreased reticulocyte count
  - WBC: decreased granulocytes and abnormal morphology (e.g. bilobed or unsegmented nuclei = Pelger abnormality)
  - platelets: thrombocytopenia, abnormalities of size and cytoplasm (e.g. giant hypogranular platelets)
- bone marrow aspirate and biopsy with cytogenetic analysis required for definitive diagnosis
  - bone marrow: dysplastic and often normocellular/hypercellular
  - cytogenetics: partial or total loss of chromosomes 5, 7, Y, or trisomy 8

MDS is a cause of macrocytic anemia

Treatment
- **low risk** of transformation to acute leukemia (IPSS-R Very Low or Low)
  - erythropoietin stimulating agents weekly is first line in reducing transfusion requirements
  - If 5q deletion based on cytogenics: lenalidomide PO
  - supportive care: RBC and platelet transfusion (consider iron chelation if frequent RBC transfusions)
- **high risk** of transformation to acute leukemia (IPSS-R Intermediate, High or Very High)
  - supportive care
  - stem cell transplantation if age <65 yr
  - epigenetic therapy: DNA methyltransferase inhibitors (e.g. 5-azacytidine), histone deacetylase inhibitors

Use of Epoetin and Darbepoetin in Patients with Cancer
Blood 2008;111:25-41
Clinical practice guideline update by American Societies of Hematology and Clinical Oncology (2007).
Initial Recommendations
1. Initiate an erythropoiesis-stimulating agent (ESA) when hemoglobin (Hb) is 100 g/L (10 g/dL) in patients with palliative chemotherapy-associated anemia to decrease the need for transfusions.
2. Discontinue ESAs when patient not responding to treatment beyond 6-8 wk.
3. Monitor iron stores and supplement iron intake for ESA-treated patients when necessary.
4. Use ESAs cautiously with chemotherapy or in patients with an elevated risk for thrombo-embolic complications.
5. It is not recommended that ESA be used for therapy in patients with cancer who are not receiving chemotherapy, as it increases thromboembolic risks and lowers survival rate. Patients with low-risk myelodysplasia are an exception.

Prognosis
- Revised International Prognostic Scoring System (IPSS-R) uses 5 factors to estimate mean survival
  - cytology, % bone marrow blasts, hemoglobin, platelets, absolute neutrophil count
  - based on the calculated score, a patient's MDS prognostic risk is "Very Low", "Low", "Intermediate", "High", or "Very High" with a mean survival of 8.7, 5.3, 3.0, 1.6, and 0.8 yr, respectively

Myeloproliferative Neoplasms

Definition
- clonal myeloid stem cell abnormalities leading to overproduction of one or more cell lines (leading to abnormalities in erythrocytes, platelets, and other cells of myeloid lineage)

Myelodysplastic Syndromes
ineffective maturation

Myeloproliferative Neoplasms
overproduction of mature cells

Epidemiology
- mainly middle-aged and older patients (peak 60-80 yr)

Prognosis
- may develop marrow fibrosis with time
- all disorders may progress to AML

Table 31. Chronic Myeloproliferative Disorders

	CML	PV	IMF	ET
Hct	↓/N	↑↑	↓	N
WBC	↑↑	↑	↑/↓	N
Plt	↑/↓	↑	↑/↓	↑↑↑
Marrow Fibrosis	±	±	+++	±
Splenomegaly	+++	+	+++	+
Hepatomegaly	+	+	++	–
Genetic Association	*bcr-abl* mut. (90+%)	JAK2 mut. (96%)	JAK2 mut. (~50%)	JAK2 mut. (~50%)

CML = chronic myeloid leukemia; ET = essential thrombocythemia; IMF = idiopathic myelofibrosis; PV = polycythemia vera

Chronic Myeloid Leukemia

Definition
- myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate

Basophilia is uncommon in other medical conditions

Epidemiology
- occurs in any age group (mostly middle age to elderly) with a median age of 65 yr

Pathophysiology
- Philadelphia chromosome (Ph)
  - translocation between chromosomes 9 and 22
  - the c-abl proto-oncogene is translocated from chromosome 9 to "breakpoint cluster region" (bcr) of chromosome 22 to produce *bcr-abl* fusion gene, an active tyrosine kinase

Clinical Features
- **3 clinical phases**
  - **chronic phase:** 85% diagnosed here
    - few blasts (<10%) in peripheral film
    - ± slightly elevated eosinophils and basophils
    - no significant symptoms
  - **accelerated phase:** impaired neutrophil differentiation
    - circulating blasts (10-19%) with increasing peripheral basophils (pruritus)
    - CBC: thrombocytopenia <100 x 10^9/L
    - cytogenetic evidence of clonal evolution
    - worsening constitutional symptoms and splenomegaly (extramedullary hematopoiesis)
  - **blast crisis:** more aggressive course, blasts fail to differentiate
    - blasts (>20%) in peripheral blood or bone marrow; reflective of acute leukemia (1/3 ALL, 2/3 AML)
- clinical presentation
  - 20-50% of patients are asymptomatic when diagnosed (incidental lab finding)
  - nonspecific symptoms
    - fatigue, weight loss, malaise, excessive sweating, fever
  - secondary to splenic involvement
    - early satiety, LUQ pain/fullness, shoulder tip pain (referred)
    - splenomegaly (most common physical finding)
  - anemia
  - bleeding: secondary to platelet dysfunction
  - pruritus, PUD: secondary to increased blood histamine
  - leukostasis, priapism, encephalopathy (rare): secondary to very elevated WBC (rare)

Investigations
- elevated WBC, decreased/normal RBC, increased/decreased platelets, increased basophils
  - WBC differential shows a bimodal distribution, with predominance of myelocytes and neutrophils
- peripheral blood film
  - leukoerythroblastic picture (immature red cells and granulocytes present, e.g. myelocytes and normoblasts)
  - presence of different mid-stage progenitor cells differentiates it from AML
- bone marrow
  - myeloid hyperplasia with left shift, increased megakaryocytes, mild fibrosis
- molecular and cytogenetic studies of bone marrow or peripheral blood for Philadelphia chromosome
- abdominal imaging for spleen size

Chronic Myeloproliferative Neoplasias: Six Year Follow-Up of Patients Receiving Imatinib for the First-Line Treatment of CML
Leukemia 2009;23:1054-1061
Study: The Randomized Study of Interferon vs. STI571 (IRIS) trial enrolled patients with chronic phase chronic myeloid leukemia (CML-CP) to either imatinib (n=533) or interferon-α (IFN) plus cytarabine (n=553).
Results: Assessing the imatinib arm specifically at the sixth year point, there were no reports of disease progression to accelerated phase (AP) or blast crisis (BC), toxicity profile was unchanged, and cytogenetic response rate was 82%. Estimated event-free survival was 83% and rate of freedom from progression to AP and BC was 93%.
Conclusion: This 6-year update of IRIS demonstrates the efficacy and safety of imatinib as first-line therapy for CML patients.

Treatment
- **symptomatic**
  - allopurinol and antihistamines
- **chronic phase**
  - imatinib mesylate inhibits proliferation and induces apoptosis by inhibiting tyrosine kinase activity in cells positive for *bcr-abl*
    - if loss of response or intolerance (~25%), trial of 2nd (dasatinib) or 3rd (nilotinib) generation inhibitors
    - dasatinib and nilotinib may also be considered for first line management
  - interferon-α: may improve response to tyrosine kinase inhibitors; typically now only used for pregnant patients
  - hydroxyurea in palliative setting to reduce WBC
- **accelerated phase or blast phase**
  - refer for clinical trial or 2nd/3rd generation TKI and prepare for allogeneic stem cell transplant patients, in blast phase typically get standard AML induction
- stem cell transplantation may be curative: to be considered in young patients who do not meet therapeutic milestones
- treatment success is monitored based on therapeutic milestones
  - hematologic: improved WBC and platelet counts, reduced basophils
  - cytogenetic: undetectable Philadelphia-chromosome in the bone marrow
  - molecular: reduction/absence of *bcr-abl* transcripts in periphery and marrow

Detection of the *bcr-abl* fusion gene is a diagnostic test for CML (present in over 90% of patients)

Prognosis
- survival dependent on response
  - those achieving complete cytogenetic response (CCR) on imatinib by 18 mo of therapy: 6 yr overall survival >90%
  - those who do NOT achieve CCR on imatinib: 6 yr overall survival of 66%
- acute phase (blast crisis – usually within 3-5 yr)
  - 2/3 develop a picture similar to AML
    - unresponsive to remission induction
  - 1/3 develop a picture similar to ALL
    - remission induction (return to chronic phase) achievable

Polycythemia Vera

Definition
- stem cell disorder characterized by elevated RBC mass (erythrocytosis) ± increased white cell and platelet production

Erythromelalgia is a pathognomonic microvascular thrombotic complication in PV and ET

Clinical Features
- symptoms are secondary to high red cell mass and hyperviscosity (see *Erythrocytosis*, H6)
- bleeding complications: epistaxis, gingival bleeding, ecchymoses, and GI bleeding
  - due to platelet abnormalities
- thrombotic complications: DVT, PE, thrombophlebitis, increased incidence of stroke, MI
  - due to increased blood viscosity, increased platelet number and/or activity
- erythromelalgia (burning pain in hands and feet and erythema of the skin)
  - associated with platelets >400 x 10^9/L
  - pathognomonic microvascular thrombotic complication in PV and ET
- pruritus, especially after warm bath or shower (40%)
  - due to cutaneous mast cell degranulation and histamine release
- epigastric distress, PUD
  - due to increased histamine from tissue basophils, alterations in gastric mucosal blood flow due to increased blood viscosity
- gout (hyperuricemia)
  - due to increased cell turnover
- characteristic physical findings
  - plethora (ruddy complexion) of face (70%), palms
  - splenomegaly (70%), hepatomegaly (40%)

Cardiovascular Events and Intensity of Treatment in Polycythemia Vera
NEJM 2013;368:22-33
Study: Prospective, RCT, mean follow-up of 28.9 mo. Blinding not described.
Population: 365 patients with JAK2-positive polycythemia vera being treated with phlebotomy, hydroxyurea, or both.
Intervention: Patients were randomized to a target hematocrit <45% (low-hematocrit group) or 45-50% (high-hemtocrit group).
Outcome: Composite of time until death from cardiovascular causes of major thrombotic events.
Results: The hazard ratio (HR) for the primary outcome was 3.91 (95% CI 1.45-10.53, p=0.007), while the HR for the primary outcome plus superficial venous thrombosis was 2.69 (95% CI 1.19-6.12, p=0.02) for the high-hematocrit vs. low-hematocrit group.
Conclusions: The hematocrit target of <45% was associated with a lower incidence of CV death, major thrombotic events, and superficial venous thrombosis in patients with polycythemia vera.

Investigations
- see *Erythrocytosis*, H6
- must rule out secondary polycythemia
- diagnosis (WHO 2008) requires either both major criteria plus one minor criteria OR the first major criterion plus 2 minor criteria
  - Major Criteria
    1. hemoglobin >185 g/L in men, >165 g/L in women or other evidence of increased red cell volume
    2. presence of JAK2 V617F or other functionally similar mutation such as JAK2 exon 12 mutation

- Minor Criteria
  1. bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
  2. serum erythropoietin level below the reference range for normal
  3. endogenous erythroid colony formation *in vitro*

Treatment
- phlebotomy to keep hematocrit <45%
- hydroxyurea (prior thrombosis or symptoms, severe coronary artery disease, refractory to phlebotomy)
- low-dose Aspirin® (for antithrombotic prophylaxis, will also treat erythromelalgia)
- allopurinol: as needed
- antihistamines: as needed

Prognosis
- 10-20 yr survival with treatment
- complicated by thrombosis, hemorrhage, leukemic transformation (AML)

Efficacy and Safety of Low-dose Aspirin® in Polycythemia Vera
NEJM 2004;350:114-124
Study: Double-blind, placebo-controlled, RCT.
Participants: 518 patients with polycythemia vera (PV) with no clear indication for, or contraindication to, ASA therapy.
Intervention: Patients received either low-dose ASA 100 mg daily (n=253) or placebo (n=265) and were followed for up to 5 yr.
Primary Outcome: Cumulative rate of (I) nonfatal MI, nonfatal stroke, or death from cardiovascular causes and the cumulative rate of (II) the previous 3 plus PE and major venous thrombosis.
Results: Primary outcomes (I) and (II) were reduced with treatment compared to placebo (RR 0.41; p=0.09 and RR 0.4; p=0.03, respectively). There were no differences in overall or cardiovascular mortality and major bleeding episodes.
Conclusion: Low-dose ASA can safely prevent thrombotic complications in patients with PV.

Idiopathic Myelofibrosis

Definition
- excessive bone marrow fibrosis leading to marrow failure
- characterized by anemia, extramedullary hematopoiesis, leukoerythroblastosis, teardrop red cells in peripheral blood and hepatosplenomegaly

Epidemiology
- rare, median age at presentation is 65 yr

Myelofibrosis can be either primary (idiopathic) or occur as a transformation of an antecedent PV or ET

Pathophysiology
- abnormal myeloid precursor postulated to produce dysplastic megakaryocytes that secrete fibroblast growth factors
  - stimulates fibroblasts and stroma to deposit collagen in marrow
- increasing fibrosis causes early release of hematopoietic precursors leading to:
  - leukoerythroblastic blood film (primitive RBCs and WBCs present in blood)
  - migration of precursors to other sites: extramedullary hematopoiesis (leading to hepatosplenomegaly)

A "leukoerythroblastic" blood film (RBC and granulocyte precursors) implies bone marrow infiltration with malignancy (e.g. leukemias, solid tumour metastases) or fibrosis (e.g. IMF)

Clinical Features
- anemia (severe fatigue is most common presenting complaint, pallor on exam in >60%)
- weight loss, fever, night sweats → secondary to hypermetabolic state
- splenomegaly (90%) → secondary to extramedullary hematopoiesis; may cause early satiety
- hepatomegaly (70%) → may get portal hypertension
- bone and joint pain → secondary to osteosclerosis, gout
- signs of extramedullary hematopoiesis (depends on organ involved)

Investigations
- CBC: anemia, variable platelets, variable WBC
- biochemistry: increased ALP (liver involvement, bone disease), increased LDH (2° to ineffective hematopoiesis), increased uric acid (increased cell turnover), increased B_{12} (2° to increased neutrophil mass)
- blood film: leukoerythroblastosis with teardrop RBCs, nucleated RBCs, variable polychromasia, large platelets, and megakaryocyte fragments
- JAK2 PCR and calreticulin PCR
- bone marrow aspirate: "dry tap" in as many as 50% of patients (no blood cells espirated)
- bone marrow biopsy (essential for diagnosis): fibrosis, atypical megakaryocytic hyperplasia, thickening and distortion of the bony trabeculae (osteosclerosis)

IMF typically has a dry BM aspirate and teardrop RBCs (aspiration gives no blood cells)

A Double-Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis
NEJM 2012;366:799-807
Study: Double-blinded RCT of 309 patients with myelofibrosis randomized to ruxolitinib or placebo.
Outcome: Primary outcome was reduction in spleen volume of >35% at 24 wk. Secondary outcomes were durability of response, symptom burden, and overall survival.
Results: A greater proportion of patients on ruxolitinib had reduction in spleen volume >35% (41.9% vs. 0.7%) and this was sustained in 67% at 48 wk. Ruxolitinib also led to greater symptom improvement (45% vs. 5.3%) and less mortality (13 vs. 24). There was no difference in rate of discontinuation due to adverse events (11.0% vs. 10.6%) but anemia and thrombocytopenia were more common with ruxolitinib.
Conclusions: Ruxolitinib reduced spleen size, improved symptoms and improved survival, compared with placebo.

Treatment
- allogeneic stem cell transplant is potentially curative
- JAK2 inhibitors
- symptomatic treatment
  - transfusion for anemia
  - erythropoietin: 30-50% of patients respond
  - androgens for anemia (e.g. danazol has shown transient response with response rates of <30%)
  - hydroxyurea for splenomegaly, thrombocytosis, leukocytosis, systemic symptoms
    - interferon-α (as second line therapy)
    - splenectomy (as third line therapy; associated with high mortality and morbidity)
  - radiation therapy for symptomatic extramedullary hematopoiesis, symptomatic splenomegaly
  - thalidomide, and etanercept may improve quality of life and spleen size, but not survival

Prognosis
- International Prognostic Scoring System (IPSS) for IMF uses 5 factors to determine mean survival
  - presence of constitutional symptoms; age >65; hemoglobin <100 g/L; leukocyte count >25,000/mm^3; circulating blast cells ≥1%
  - based on the calculated score, a patient's IMF is categorized as "low", "intermediate 1", "intermediate 2", or "high" with a mean survival of 135, 95, 48, and 27 mo respectively
- risk of transformation to AML (8-10%)

Essential Thrombocythemia

Definition
- overproduction of platelets in the absence of recognizable stimulus
- must rule out secondary thrombocythemia

Epidemiology
- increases with age; F:M = 2:1, but F=M at older age

Diagnosis (2008 WHO Criteria) requires meeting all four criteria:
1. sustained platelet count >450 x 10^9/L
2. bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased number of enlarged, mature megakaryocytes; no significant increase or left shift of neutrophil granulopoiesis or erythropoiesis
3. not meeting WHO criteria for PV, primary myelofibrosis, *bcr-abl* CML, or myelodysplastic syndrome or other myeloid neoplasms
4. demonstration of JAK2 V617F or calreticulin (or in its absence another clonal marker), no evidence for reactive thrombocytosis

Clinical Features
- often asymptomatic
- vasomotor symptoms (40%)
  - headache (common), dizziness, syncope
  - erythromelalgia (burning pain of hands and feet, dusky colour, usually worse with heat, caused by platelet activation → microvascular thrombosis)
- thrombosis (arterial and venous)
- bleeding (often GI; associated with platelets >1,000 x 10^9/L)
- constitutional symptoms, splenomegaly
- pregnancy complications; increased risk of spontaneous abortion
- risk of transformation to AML (0.6-5%), myelofibrosis

Investigations
- CBC: increased platelets; may have abnormal platelet aggregation studies
- JAK2 PCR assay
- bone marrow hypercellularity, megakaryocytic hyperplasia, giant megakaryocytes
- increased K^+, increased PO_4^{3-} (2° to release of platelet cytoplasmic contents)
- diagnosis: exclude other myeloproliferative disorders and reactive thrombocytosis

Treatment
- low dose ASA if previous history of thrombotic event, ≥1 cardiovascular risk factors, older, or symptomatic
- cytoreductive therapy if thrombosis or thrombotic symptoms: hydroxyurea (HU) (1st line therapy), anagrelide, interferon-α, or ^{32}P (age >80 or lifespan <10 yr)
- splenectomy not recommended (increased risk of bleeding episodes, thrombosis)

Etiology of Secondary Thrombocythemia
- Infection
- Inflammation (IBD, arthritis)
- Malignancy
- Hemorrhage
- Iron deficiency
- Hemolytic anemia
- Post splenectomy
- Post chemotherapy

Anagrelide vs. Hydroxyurea for Essential Thrombocythemia: ANAHYDRET Study, A Randomized Controlled Trial
Blood 2013;121:1720-8
Study: Prospective, non-inferiority, RCT. Majority of patients followed beyond 1 yr.
Population: 259 previously untreated, high-risk patients with essential thrombosis as per the WHO guidelines.
Intervention: Patients were randomized to receive either non-immediate release formulation of anagrelide or hydroxyurea.
Outcome: Examined platelet counts, hemoglobin levels, leukocyte counts, and occurrence of ET-related events.
Results: The hazard ratio (HR) of developing thrombocythemia was 1.19 (95% CI 0.61-2.30). The HR for a reduction of hemoglobin was 1.03 (95% CI 0.57-1.81), and 0.92 (95% CI 0.57-1.46) for leukocytosis. There was no statistical difference in occurrence of major or minor arterial or venous thrombosis, severe or minor bleeding events, or rate of discontinuation between the two arms.
Conclusions: In patients with ET, anagrelide is non-inferior to hydroxyurea in the prevention of thrombotic complications.

There is an asymptomatic "benign" form of essential thrombocythemia with a stable or slowly rising platelet count; treatment includes observation, ASA, sulfinpyrazone, or dipyridamole

Lymphoid Malignancies

Acute Lymphoblastic Leukemia

Definition
- malignant disease of the bone marrow in which early lymphoid precursors proliferate and replace the normal hematopoietic cells of the marrow
- WHO subdivides ALL into two types depending on cell of origin
  1. B-cell: precursor B lymphoblastic leukemia
  2. T-cell: precursor T lymphoblastic leukemia
- the French-American-British (FAB) classification (L1, L2, L3) is no longer encouraged, as morphology is not prognostic

75% of ALL occurs in children <6 yr old; second peak at age 40

Clinical Features
- see *Acute Myeloid Leukemia*, H37 for full list of symptoms
- distinguish ALL from AML based on Table 32
- clinical symptoms usually secondary to:
  - **bone marrow failure:** anemia, neutropenia (50% present with fever; also infections of oropharynx, lungs, perianal region), thrombocytopenia
  - **organ infiltration:** tender bones, lymphadenopathy, hepatosplenomegaly, meningeal signs (headache, N/V, visual symptoms; especially in ALL relapse)

Investigations
- CBC: increased leukocytes >10 x 10^9/L (occurs in 50% of patients); neutropenia, anemia, or thrombocytopenia
- may have increased uric acid, K^+, PO_4^{3-}, Ca^{2+}, LDH
- PT, aPTT, fibrinogen, D-dimers for DIC
- leukemic lymphoblasts lack specific morphological (no granules) or cytochemical features, therefore diagnosis depends on immunophenotyping
- cytogenetics: Philadelphia (Ph) chromosome in ~25% of adult ALL cases
- CXR: patients with ALL may have a mediastinal mass
- LP prior to systemic chemotherapy to assess for CNS involvement (ensure adequate platelet count and PT/PTT)

Treatment
- eliminate abnormal cloned cells
  1. **Induction:** to induce complete remission (undetectable leukemic blasts, restore normal hematopoiesis)
  2. **Consolidation and/or intensification of chemotherapy**
     - consolidation: continuing same chemotherapy to eliminate subclinical leukemic cells
     - intensification: high doses of different (non-cross-reactive) chemotherapy drugs to eliminate cells with resistance to primary treatment
  3. **Maintenance chemotherapy:** low dose intermittent chemotherapy over prolonged period (2-3 yr) to prevent relapse
  4. **Prophylaxis:** CNS radiation therapy or methotrexate (intrathecal or systemic)
- hematopoietic stem cell transplantation: potentially curative (due to pre-implant myeloablative chemoradiation and post-implant graft-versus-leukemia effect) but relapse rates and non-relapse mortality high

Treatment of ALL vs. AML
- No proven benefit of maintenance chemotherapy in AML
- No routine CNS prophylaxis in AML

Prognosis
- depends on response to initial induction or if remission is achieved following relapse
- good prognostic factors: young, WBC <30 x 10^9/L, T-cell phenotype, absence of Ph chromosome, early attainment of complete remission
- achievement of first remission: 60-90%
- childhood ALL: 80% long-term remission (>5 yr)
  - higher cure rates in children because of better chemotherapy tolerance, lower prevalence of *bcr-abl* fusion gene (associated with chemotherapeutic resistance)
- adult ALL: 30-40% 5-yr survival

Table 32. Differentiating AML From ALL

AML	ALL
Big people (adults)	Small people (kids)
Big blasts	Small blasts
Big mortality rate	Small mortality rate (kids)
Lots of cytoplasm	Less cytoplasm
Lots of nucleoli (3-5)	Few nucleoli (1-3)
Lots of granules and Auer rods	No granules
Myeloperoxidase, Sudan black stain	PAS (periodic acid-Schiff)
Maturation defect beyond myeloblast or promyelocyte	Maturation defect beyond lymphoblast

To Differentiate AML From ALL:
Remember **Big** and Sm**ALL**

Lymphomas

Definition
- collection of lymphoid malignancies in which malignant lymphocytes accumulate at lymph nodes and lymphoid tissues
  - leading to lymphadenopathy, extranodal disease, and constitutional symptoms

American Society of Hematology Choosing Wisely Recommendation
Limit surveillance CT scans in asymptomatic patients after curative-intent treatment for aggressive lymphoma

Table 33. Ann Arbor System for Staging Lymphomas

Stage	Description
I	Involvement of a single lymph node region or extralymphatic organ or site
II	Involvement of two or more lymph node regions or an extralymphatic site and one or more lymph node regions on same side of diaphragm
III	Involvement of lymph node regions on both sides of the diaphragm; may or may not be accompanied by single extra lymphatic site or splenic involvement
IV	Diffuse involvement of one or more extralymphatic organs including bone marrow

- subtypes
  - A = absence of B-symptoms (see *Approach to Lymphadenopathy*, H12)
  - B = presence of B-symptoms

- Ann Arbor staging can be used for both Hodgkin and non-Hodgkin lymphoma, but grade/histology is more important for non-Hodgkin lymphoma because the outcome differs significantly depending on type of lymphoma
- Prognostic scores are different for indolent versus aggressive lymphomas
- Highly aggressive lymphomas act like acute leukemias

Table 34. Chromosome Translocations

Translocation	Gene Activation	Associated Neoplasm
t(8;14)	c-myc activation	Burkitt's lymphoma
t(14;18)	bcl-2 activation	Follicular lymphoma
t(9;22)	Philadelphia chromosome (*bcr-abl* hybrid)	CML, ALL in adults (25% of the time)
t(11;14)	Overexpression of cyclin D1 protein	Mantle cell lymphoma
t(15;17)	Activation of retinoic acid receptor alpha	Acute promyelocytic leukemia

Hodgkin Lymphoma

Hodgkin is distinguished from non-Hodgkin lymphoma by the presence of Reed-Sternberg cells

Definition

- malignant proliferation of lymphoid cells with Reed-Sternberg cells (thought to arise from germinal centre B-cells)

Epidemiology

- bimodal distribution with peaks at 20 yr and >50 yr
- association with Epstein-Barr virus in up to 50% of cases, causal role not determined

Hodgkin lymphoma classically presents as a painless, non-tender, firm, rubbery enlargement of superficial lymph nodes, most often in the cervical region

Clinical Features

- asymptomatic lymphadenopathy (70%)
  - non-tender, rubbery consistency
  - cervical/supraclavicular (60-80%), axillary (10-20%), inguinal (6-12%)
- splenomegaly (50%) ± hepatomegaly
- mediastinal mass
  - found on routine CXR, may be symptomatic (cough)
  - rarely may present with SVC syndrome, pleural effusion
- systemic symptoms
  - B symptoms (especially in widespread disease; fever in 30%), pruritus
- non-specific/paraneoplastic
  - alcohol-induced pain in nodes, nephrotic syndrome
- starts at a single site in lymphatic system (node), spreads first to adjacent nodes
  - disease progresses in contiguity with lymphatic system

Investigations

- CBC
  - anemia (chronic disease, rarely hemolytic), eosinophilia, leukocytosis, platelets normal or increased early, decreased in advanced disease
- biochemistry
  - HIV serology
  - LFTs (liver involvement)
  - renal function tests (prior to initiating chemotherapy)
  - ALP, Ca^{2+} (bone involvement)
  - ESR, LDH (monitor disease progression)
- imaging
  - CXR, CT chest (lymph nodes, mediastinal mass), CT abdomen/pelvis (liver or spleen involvement), gallium scan (assess treatment response), PET scans
  - cardiac function assessment (MUGA scan or echocardiography): for patients at high risk of pre-treatment cardiac disease (age >60, history of HTN, CHF, PUD, CAD, MI, CVA), treatment can be cardiotoxic
  - PFTs: if history of lung disease (COPD, smoking, previous radiation to lung)
- excisional lymph node biopsy confirms diagnosis
- bone marrow biopsy to assess marrow infiltration (only necessary if B-symptoms, stage III or IV, bulky disease or cytopenia)

Treatment
- stage I-II: chemotherapy (ABVD) followed by involved field radiotherapy (XRT)
- stage III-IV: chemotherapy (ABVD) with XRT for bulky disease
- relapse, resistant to therapy: high dose chemotherapy, bone marrow transplant
  - new imaging modalities increasingly used including PET scans (follow treatment response)

Treatment of HL depends on stage; treatment of NHL depends on histologic subtype.

Complications of Treatment
- cardiac disease: secondary to XRT, adriamycin is also cardiotoxic
- pulmonary disease: secondary to bleomycin (interstitial pneumonitis)
- infertility: recommend sperm banking
- secondary malignancy in irradiated field
  - <2% risk of MDS, AML (secondary to treatment, usually within 8 yr)
  - solid tumours of lung, breast; >8 yr after treatment
  - non-Hodgkin lymphoma
- hypothyroidism: post XRT

Prognosis
- Hasenclever adverse prognostic factors:
  1. serum albumin <40 g/L
  2. hemoglobin <105 g/L
  3. male
  4. stage IV disease
  5. age ≥45 yr
  6. leukocytosis (WBC >1.5 x 10^9/L)
  7. lymphocytopenia (lymphocytes <0.06 x 10^9/L or <8% of WBC count or both)
- prognostic score
  - each additional adverse prognostic factor decreases freedom from progression at 5 yr (FFP)

International Prognostic Factors Project 1998

Prognostic Factors	FFP
0	84%
1	77%
2	67%
3	60%
4	51%
5-7	42%

FFP = freedom from progression at 5 yr

Non-Hodgkin Lymphoma

Definition
- malignant proliferation of lymphoid cells of progenitor or mature B- or T-cells

Classification
- multiple classification systems exist at present and may be used at different centres
- can originate from both B- (85%) and T- or NK- (15%) cells
  - B-cell NHL: e.g. diffuse large B-cell lymphoma, follicular lymphoma, Burkitt's lymphoma, mantle cell lymphoma
  - T-cell NHL: e.g. mycosis fungoides, anaplastic large cell lymphoma
- WHO/REAL classification system: 3 categories of NHLs based on natural history
  - **indolent** (35-40% of NHL): e.g. follicular lymphoma, small lymphocytic lymphoma/CLL, mantle cell lymphoma
  - **aggressive** (~50% of NHL): e.g. diffuse large B-cell lymphoma
  - **highly aggressive** (~5% of NHL): e.g. Burkitt's lymphoma

Clinical Features
- painless superficial lymphadenopathy, usually >1 lymph node region
- usually presents as widespread disease (exception is aggressive lymphoma)
- constitutional symptoms not as common as in Hodgkin lymphoma
- cytopenia: anemia ± neutropenia ± thrombocytopenia can occur when bone marrow is involved
- abdominal signs
  - hepatosplenomegaly
  - retroperitoneal and mesenteric involvement (second most common site of involvement)
- oropharyngeal involvement in 5-10% with sore throat and obstructive apnea
- extranodal involvement: most commonly GI tract; also testes, bone, kidney
- CNS involvement in 1% (often with HIV)

NHL: Associated Conditions
- Immunodeficiency (e.g. HIV)
- Autoimmune diseases (e.g. SLE)
- Infections (e.g. EBV)

Investigations
- CBC
  - normocytic normochromic anemia
  - autoimmune hemolytic anemia
  - advanced disease: thrombocytopenia, neutropenia, and leukoerythroblastic anemia
- peripheral blood film may show lymphoma cells
- flow cytometry of peripheral blood is valuable for low-grade NHL
- biochemistry
  - increase in uric acid
  - abnormal LFTs in liver metastases
  - increased LDH (rapidly progressing disease, poor prognostic factor)
- CXR, CT neck, abdomen, pelvis for staging

- PET is useful for monitoring response to treatment and evaluation of residual tumour following therapy in aggressive histological disease
- diagnosed by
  - lymph node biopsy: excisional biopsy preferred, FNA unreliable
  - bone marrow biopsy: not optimal for diagnosis as BM may not be involved

Treatment

- localized disease (e.g. GI, brain, bone, head and neck)
  - radiotherapy to primary site and adjacent nodal areas
  - adjuvant chemotherapy
  - surgery: splenic marginal zone lymphoma
- **indolent lymphoma:** goal of treatment is symptom management
  - watchful waiting
  - radiation therapy for localized disease
  - bendamustine plus rituximab, an anti-CD20 antibody, is superior to CHOP + rituximab (CHOP-R) for advanced stage disease (StIL trial)
- **aggressive lymphoma:** goal of treatment is curative
  - combination chemotherapy: CHOP is mainstay, plus rituximab if B-cell lymphoma
  - radiation for localized/bulky disease
  - CNS prophylaxis with high-dose methotrexate if certain sites involved (testicular, nasopharyngeal)
  - relapse, resistant to therapy: high dose chemotherapy, BMT
- **highly aggressive lymphoma**
  - Burkitt lymphoma: short bursts of intensive chemotherapy "CODOX-M" chemotherapy regimen also often used ± IVAC with Rituximab
  - CNS prophylaxis and tumour lysis syndrome prophylaxis

Complications

- hypersplenism
- infection
- autoimmune hemolytic anemia and thrombocytopenia
- vascular obstruction (from enlarged nodes)
- bowel perforation
- tumour lysis syndrome (particularly in very aggressive lymphoma) see *Tumour Lysis Syndrome* H52

Prognosis

- follicular lymphoma: Follicular Lymphoma International Prognostic Index is used (5 adverse prognostic factors): age >60; >4 nodal areas; elevated LDH; Ann Arbor stage III-IV; hemoglobin <120 g/L
  - based on calculated risk, mean 5 yr survival ranges from 53-91%
  - rarely curative, typically relapsing and remitting course with risk of transformation to aggressive lymphoma such as diffuse large B-cell lymphoma
- diffuse large B-cell lymphoma: The International Prognostic Factor Index is used (5 adverse prognostic factors): age >60; Ann Arbor stage (III-IV); performance status (ECOG/Zubrand 2-4); elevated LDH; >1 extranodal site
  - based on calculated risk, mean 5 yr survival ranges from 26-73%
  - ~40% rate of cure

Table 35. Characteristics of Select Non-Hodgkin Lymphomas

	Follicular Lymphoma	Diffuse Large B-Cell Lymphoma (DLBCL)	Burkitt Lymphoma	Mantle Cell Lymphoma
Percentage of NHLs	22-30%	33%	<1% adult NHLs 30% childhood NHLs	6%
Genetic Mutation	Bcl-2 activation	Bcl-2, Bcl-6, MYC rearrangements	c-myc activation	Overexpression of cyclin D1 (Bcl-1 activation)
Classification	Indolent	Aggressive (high-grade)	Very aggressive	Indolent
Risk Factors	Middle-age – elderly	Previous CLL (Richter's transformation: 5% CLL patients progress to DLBCL)	1. Endemic: African origin, EBV-associated 2. Sporadic: no EBV 3. HIV-related: AIDS-defining illness	Male (M:F = 4:1)
Clinical Features	• Widespread painless LAD* ± bone marrow involvement • Frequent transformation to aggressive lymphoma • Very responsive to chemoradiation treatment	• Rapidly progressive LAD and extranodal infiltration • 50% present at stage I/II, 50% widely disseminated	• Endemic form: massive jaw LAD • "Starry-sky" histology • High risk of tumour lysis syndrome upon treatment	• Often presents Stage IV with palpable LAD • Involvement of GI tract (lymphomatosis polyposis), Waldeyer's Ring • 5 yr survival 25%

*LAD = lymphadenopathy

Common Chemotherapeutic Regimens

CHOP: cyclophosphamide, hydroxydoxorubicin (Adriamycin®), vincristine (Oncovin®), prednisone

VAD: vincristine, adriamycin, dexamethasone

ABVD: adriamycin, bleomycin, vinblastine, dacarbazine

BEACOPP: bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone

CHOP-Like Chemotherapy With or Without Rituximab in Young Patients with Good-Prognosis Diffuse Large B-Cell Lymphoma (MInT)

Lancet Oncol 2011;12:1013-1022

Study: International RCT with a median follow-up of 72 mo.

Participants: 824 patients with good-prognosis diffuse large B-cell lymphoma who had ≤1 risk factor, stage II-IV disease, or stage I disease with bulk (age 18-60 yr).

Intervention: Patients received either 6 cycles of CHOP-like chemotherapy and rituximab (CCR; n=413) or 6 cycles of CHOP-like chemotherapy alone (CLC; n=411). Bulky and extranodal sites received additional radiotherapy.

Primary Outcome: Event-free survival.

Results: Patients receiving CCR had an increased 6 yr event-free survival compared with the CLC group (74.3% vs. 55.8%; p<0.0001). Event-free survival was affected by treatment group, presence of bulky disease, and age-adjusted International Prognostic Index (IPI). Overall survival was affected by treatment group and presence of bulky disease. Within the CCR group, a favourable subgroup (IPI=0, no bulk) and less favourable subgroup (IPI=1 or bulk, or both) could be defined; event-free survival was 84.3% vs. 71.0%.

Conclusion: Rituximab added to six cycles of CHOP is an effective treatment for young patients with good-prognosis diffuse large B-cell lymphoma. The definition of two prognostic subgroups based on IPI and disease bulk allows a more refined therapeutic approach to these patients.

Malignant Clonal Proliferations of Mature B-Cells

Table 36. Characteristics of B-Cell Malignant Proliferation

	CLL	Macroglobulinemia	Myeloma
Cell Type	Lymphocyte	Plasmacytoid	Plasma cell
Protein	IgM if present	IgM	IgG, A, light chain (rarely M, D, or E)
Lymph Nodes	Very common	Common	Rare
Hepatosplenomegaly	Common	Common	Rare
Bone Lesions	Rare	Rare	Common
Hypercalcemia	Rare	Rare	Common
Renal Failure	Rare	Rare	Common
Immunoglobulin Complications	Common	Rare	Rare

Rouleaux formation on peripheral blood smear, if not artifact, denotes hyperglobulinemia (but not necessarily monoclonality)

Chronic Lymphocytic Leukemia


Definition
- indolent disease characterized by clonal malignancy of mature B-cells

Epidemiology
- most common leukemia in Western world
- mainly older patients; median age 65 yr
- M>F

Pathophysiology
- accumulation of neoplastic lymphocytes in blood, bone marrow, lymph nodes, and spleen

Clinical Features
- 25% asymptomatic (incidental finding)
- 5-10% present with B-symptoms (≥1 of: unintentional weight loss ≥10% of body weight within previous 6 mo, temperature >38°C or night sweats for ≥2 wk without evidence of infection, extreme fatigue)
- lymphadenopathy (50-90%), splenomegaly (25-55%), hepatomegaly (15-25%)
- immune dysregulation: autoimmune hemolytic anemia (Coombs positive), ITP, hypogammaglobulinemia ± neutropenia
- bone marrow failure: late, secondary to marrow involvement by CLL cells

Investigations
- CBC: clonal population of CLL lymphocytes >5 x 10^9/L
- peripheral blood film
  - lymphocytes are small and mature
  - smudge cells
- flow cytometry (CD5, CD20, CD23, etc.)
- cytogenetics: FISH (dictates response therapy and prognosis)
- bone marrow aspirate
  - lymphocytes >30% of all nucleated cells
  - infiltration of marrow by lymphocytes in 4 patterns: nodular (10%), interstitial (30%), diffuse (35%, worse prognosis), or mixed (25%)

Smudge cells are artifacts of damaged lymphocytes from slide preparation

Natural History and Treatment
- natural history: indolent and incurable; most cases show slow progression
- small minority present with aggressive disease; usually associated with chromosomal abnormalities (e.g. p53 deletion)
- first line therapy is dictated by cytogenetic status and patient co-morbidities
  - observation if early, stable, asymptomatic treatment options vary by region; ideal first line theraepy should include a monoclonal CD20 agent (e.g. rituximab, ofatumumab, obinotuzumab)
    - commonly fludarabine + cyclophosphamide+ rituximab (FCR) in fit patients with normal CrCl; bendamustine + rituximab (BR) in less fit
    - chlorambucil + anti-CD20 in the elderly
  - corticosteroids, IVIg: especially for autoimmune phenomenaradiotherapy

- molecular therapies
  - Idelalisib – PI3K inhibitor
  - Ibrutinib – BTK (Bruton's tyrosine kinase) inhibitor

Prognosis
- 9 yr median survival, but varies greatly
- prognosis predicted by Rai staging and cytogenetic status
  - low risk: lymphocytosis in blood and bone marrow only
  - intermediate risk: lymphocytosis with enlarged nodes in any site or splenomegaly, hepatomegaly
  - high risk: lymphocytosis with disease-related anemia (<110 g/L) or thrombocytopenia (<100 x 10^9/L)

Complications
- bone marrow failure
- immune complications: AIHA, ITP, immune deficiency (hypogammaglobulinemia, impaired T-cell function)
- polyclonal or monoclonal gammopathy (often IgM)
- hyperuricemia with treatment
- 5% undergo Richter's transformation: aggressive transformation to diffuse large B-cell lymphoma (see Table 35)

Multiple Myeloma

Definition
- neoplastic clonal proliferation of plasma cells producing a monoclonal immunoglobulin resulting in end organ dysfunction
- usually single clone of plasma cells, although biclonal myeloma also occurs; rarely non-secretory

Epidemiology
- incidence 3 per 100,000, most common plasma cell malignancy
- increased frequency with age; median age of diagnosis is 68 yr; M>F

Pathophysiology
- malignant plasma cells secrete monoclonal antibody
  - 95% produce M protein (monoclonal Ig = identical heavy chain + identical light chain, or light chains only)
    - IgG 50%, IgA 20%, IgD 2%, IgM 0.5%
    - 15-20% produce free light chains or light chains alone found in either:
      - serum as an increase in the quantity of either kappa or lambda light chain (with an abnormal kappa:lambda ratio)
      - urine has Bence-Jones protein
  - <5% are non-secretors

Clinical Features and Complications
- bone disease: pain (usually back), bony tenderness, pathologic fractures
  - lytic lesions are classical (skull, spine, proximal long bones, ribs)
  - increased bone resorption secondary to osteoclast activating factors such as PTHrP
- anemia: weakness, fatigue, pallor
  - secondary to bone marrow suppression
- weight loss
- infections
  - usually *S. pneumoniae* and Gram-negatives
  - secondary to suppression of normal plasma cell function
- hypercalcemia: N/V, confusion, constipation, polyuria, polydipsia
  - secondary to increased bone turnover
- renal disease/renal failure
  - most frequently causes cast nephropathy (see Nephrology, NP31)
- bleeding
  - secondary to thrombocytopenia, may see petechiae, purpura
  - can also be caused by acquired von Willebrand disease
- extramedullary plasmacytoma
  - soft tissue mass composed of monoclonal plasma cells, purplish colour
- hyperviscosity: may manifest as headaches, stroke, angina, MI
  - secondary to increased viscosity caused by M protein

Multiple Myeloma

CRAB
Increased **C**alcium
Renal failure
Anemia
Bony lesions (lytic lesions or osteoporosis felt to be caused by myeloma)

Amyloid

The general term for a variety of proteinaceous materials that have a similar structural organization and are abnormally deposited in tissues

Found in a variety of clinical disorders and can cause systemic (e.g. MM [light chains]) or localized amyloidosis (e.g. Alzheimer disease [AB amyloid])

- amyloidosis
  - accumulation of insoluble fibrillar protein (Ig light chain) in tissues; can cause infiltration of any organ system: cardiac infiltration – diastolic dysfunction, cardiac arrhythmias, syncope, sudden death; GI involvement – malabsorption, beefy large or laterally scalloped tongue; neurologic involvement – orthostatic hypotension, carpal tunnel syndrome
  - may cause Factor X deficiency if fibrils bind Factor X → bleeding (raccoon eyes)
- neurologic disease: muscle weakness, pain, paresthesias
  - radiculopathy caused by vertebral fracture, extramedullary plasmacytoma
  - spinal cord compression (10-20% of patients) is a medical emergency

Investigations

- CBC
  - normocytic anemia, thrombocytopenia, leukopenia
  - rouleaux formation on peripheral film
- biochemistry
  - increased Ca^{2+}, increased ESR, decreased anion gap, increased Cr, albumin, β_2-microglobulin (as part of staging), proteinuria (24 h urine collection)
- monoclonal proteins
  - serum protein electrophoresis (SPEP): demonstrates monoclonal protein spike in serum in 80% (i.e. M protein)
  - urine protein electrophoresis (UPEP): demonstrates light chains in urine = Bence-Jones protein (15% secrete only light chains)
  - immunofixation: demonstrates M protein and identifies Ig type; also identifies light chains
  - serum free light chain quantification: kappa and lambda light chains, calculated ratio
- bone marrow aspirate and biopsy
  - often focal abnormality, greater than 10% plasma cells, abnormal morphology, clonal plasma cells; send for FISH or cytogenetics (prognostic implications)
- skeletal series (x-rays), MRI if symptoms of cord compression
  - presence of lytic lesions and areas at risk of pathologic fracture
  - bone scans are not useful since they detect osteoblast activity
- β_2-microglobulin, LDH, and CRP are poor prognosticators

Routine urinalysis will not detect light chains as dipstick detects albumin. Need sulfosalicylic acid or 24 h urine protein for immunofixation or electrophoresis

Light Chain Disease
15% of MM produce only light chains. Renal failure is a major problem. Kappa > lambda light chain has better prognosis

Diagnosis

- International Myeloma Working Group Criteria
  1. serum or urinary monoclonal protein
  2. presence of clonal plasma cells in bone marrow or a plasmacytoma
  3. presence of end-organ damage related to plasma cell dyscrasia, such as:
     - increased serum Ca^{2+}
     - lytic bone lesions
     - anemia
     - renal failure

Treatment

- treatment is non-curative
- treatment goals
  - improvement in quality of life (improve anemia, reverse renal failure, bony pain)
  - prevention of progression and complications
  - increase overall survival
- autologous stem cell transplant if <65 yr old
  - usually preceded by 4-6 mo of cytoreductive therapy: steroid based with novel agents
  - (i.e. immunomodulatory drugs or proteasome inhibitors)
- chemotherapy if >65 yr old or transplant-ineligible
  - melphalan, prednisone, and novel agent (i.e. bortezomib)
- dexamethasone and bortezomib if ARF; bortezomib ± dexamethasone in light chain amyloidosis
- supportive management
  - bisphosphonates for those with osteopenia or lytic bone lesions (requires renal dosing)
  - local XRT for bone pain, spinal cord compression
  - kyphoplasty for vertebral fractures to improve pain relief and regain height
  - treat complications: hydration for hypercalcemia and renal failure, bisphosphonates for severe hypercalcemia, prophylactic antibiotics, erythropoietin for anemia, DVT prophylaxis
- all patients will relapse; choice of retreatment regimen depends on duration of remission, organ involvement, patient's comorbidities, and preferences

Prognosis

- International Staging System (β_2-microglobulin and albumin) used to stage and estimate prognosis
  - cytogenetic profile (i.e. p53 mutation associated with poor survival and resistance to chemotherapy)
- median survival based on stage, usually 3-7 yr

Monoclonal Gammopathy of Unknown Significance

Definition
- presence of M protein in serum in absence of any clinical or laboratory evidence of a plasma cell dyscrasia or lymphoproliferative disorders
  - incidence: 0.15% in general population, 5% of people >70 yr of age
  - asymptomatic

Diagnosis
- presence of a serum monoclonal protein (M protein) at a concentration <30 g/L
- <10% plasma cells in bone marrow
- absence of hyperCalcemia, Renal insufficiency, Anemia, Bony disease related to the plasma cell proliferative process (absence of "CRAB")
- 0.3-1% of patients develop a hematologic malignancy each yr
  - patients with M protein peak ≥15 g/L or patients with IgA or IgM MGUS are at higher risk of malignant transformation
  - patients with abnormal serum free light chains ratio are at increased risk of malignant transformation
- monitor with annual history, physical, CBC, Cr, calcium, albumin, serum protein electrophoresis (considered pre-malignant)

Serum Free Light Chain Ratio is an Independent Risk Factor for Progression in MGUS
Blood 2005;106:812-817
Purpose: To determine whether the presence of monoclonal free kappa or lambda immunoglobulin light chains in MGUS increases the risk of progression to malignancy.
Methods: Retrospective study with median follow-up of 15 yr. Baseline serum samples obtained from 1,383 MGUS patients seen at the Mayo clinic between 1960-1994. 1,148 baseline samples were obtained within 30 d of diagnosis.
Results: Malignant progression had occurred in 87 (7.6%) patients. In 379 (33%) patients, an abnormal serum free light chain (FLC) ratio was detected. There was a significantly higher risk of progression in patients with an abnormal FLC ratio relative to patients with a normal ratio (hazard ratio, 3.5; 95% CI 2.3-5.5; p<0.001). This finding was independent of the size and type of the serum monoclonal (M) protein. In high-risk MGUS patients (abnormal serum FLC ratio, non-IgG MGUS, high serum M protein level [≥1.5 gm/dL]), the risk of progression at 20 yr was 58% compared to 37% in high-intermediate-risk MGUS (two risk factors), 21% low-intermediate risk (with one risk factor) and 5% low-risk (no risk factors).
Conclusions: The presence of an abnormal FLC ratio is a clinically and statistically significant predictor of progression in MGUS. The low-risk subset of patients with MGUS accounts for 40% of all MGUS patients and have a small lifetime risk of progression, thus less follow-up can be justified.

Lymphoplasmacytic Lymphoma (Waldenstrom's Macroglobulinemia)

Definition
- proliferation of lymphoplasmacytoid cells
  - presence of monoclonal IgM paraprotein

Clinical Features
- chronic disorder of elderly patients; median age 64 yr
- symptoms: weakness, fatigue, bleeding (oronasal), weight loss, recurrent infections, dyspnea, CHF (triad of anemia, hyperviscosity, plasma volume expansion), neurological symptoms, peripheral neuropathy, cerebral dysfunction
- signs: pallor, splenomegaly, hepatomegaly, lymphadenopathy, retinal lesions
- key complication to avoid: hyperviscosity syndrome
  - because IgM (unlike IgG) confined largely to intravascular space

Waldenstrom's macroglobulinemia accounts for 85% of all cases of hyperviscosity syndrome

Investigations and Diagnosis
- bone marrow shows plasmacytoid lymphocytes
- bone lesions usually not present
- blood work rarely see hypercalcemia
- cold hemagglutinin disease possible: Raynaud's phenomenon, hemolytic anemia precipitated by cold weather
- normocytic anemia, rouleaux, high ESR if hyperviscosity not present

Treatment
- Bendamustine – R/R-CVP chemotherapy, alkylating agents (chlorambucil), nucleoside analogues (fludarabine), rituximab, or combination therapy
- corticosteroids
- plasmapheresis for hyperviscosity: acute reduction in serum IgM

Complications of Hematologic Malignancies

Hyperviscosity Syndrome

Definition
- refers to clinical sequelae of increased blood viscosity (when relative serum viscosity >5-6 units), resulting from increased circulating serum Igs or from increased cellular blood components in hyperproliferative disorders (e.g. multiple myeloma, leukemia, PV)
- Waldenstrom's macroglobulinemia accounts for 85% of cases

Clinical Features
- hypervolemia causing: CHF, headache, lethargy, dilutional anemia
- CNS symptoms due to decreased cerebral blood flow: headache, vertigo, ataxia, stroke
- retina shows venous engorgement and hemorrhages
- bleeding diathesis
  - due to impaired platelet function, absorption of soluble coagulation factors (e.g. nasal bleeding, oozing gums)
- ESR usually very low

Treatment
- plasmapheresis, chemotherapy

Tumour Lysis Syndrome

Definition
- group of metabolic complications that result from spontaneous or treatment-related breakdown of cancer cells
- more common in diseases with large tumour burden and high proliferative rate (high grade lymphoma, leukemia)

Clinical Features
- metabolic abnormalities
  - cells lyse, releasing K^+, uric acid, PO_4^{3-} (increased levels)
  - PO_4^{3-} binds Ca^{2+} (decreased Ca^{2+})
- complications
  - lethal cardiac arrhythmia (increased K^+)
  - acute renal failure (urate nephropathy, see Nephrology, NP31)

Treatment
- prevention
  - aggressive IV hydration
  - alkalinization not recommended due to risk of calcium phosphate or xanthine precipitation in renal tubules
  - allopurinol or rasburicase
  - correction of pre-existing metabolic abnormalities
- dialysis

Blood Products and Transfusions

Blood Products

- RBCs, platelets and coagulation factors (frozen plasma [FP], cryoprecipitate, factor concentrates) are available for transfusion
- donated blood (1 U = 450-500 mL) is fractionated into these various components
  - centrifugation separates whole blood into RBCs and platelet-rich plasma
  - platelet-rich plasma is further fractionated into platelets and plasma
    - need to pool together multiple units to obtain therapeutic amounts
    - FP (previously known as FFP) is plasma frozen within 24 h of collection
    - cryoprecipitate is the high MW precipitate generated when FP is thawed at low temperatures

Blood Groups

Group	Antigen (on RBC)	Antibody (in serum)
O	H	Anti-A, anti-B
A	A	Anti-B
B	B	Anti-A
AB	A and B	Nil

Specialized Products
- irradiated blood products
  - prevent proliferation of donor T-cells in potential or actual bone marrow transplant recipients
  - used for immunocompromised patients or for patients on purine analogue chemotherapy, first-degree relatives, HLA-matched products and intrauterine transfusions, Hodgkin lymphoma
- CMV-negative blood products
  - potential transplant recipients
  - neonates
  - AIDS patients
  - seronegative pregnant women

In Canada, blood products are leukodepleted via filtration immediately after donation; therefore it is considered:
- Low in lymphokines, resulting in a lower incidence of febrile nonhemolytic transfusion reactions
- CMV negative (because CMV is found in leukocytes)

Red Blood Cells

Packed Red Blood Cells
- stored at 4°C
- transfuse within 42 d of collection, otherwise cell lysis may result in hyperkalemia
- infuse each unit over 2 h (max of 4 h)

Indications for Packed RBC Transfusion
- Hb <70 g/L; this may change as per patient's tolerance or symptoms
  - maintain Hb between 70 and 100 g/L during active bleeds
- consider maintaining a higher Hb for patients with:
  - CAD/unstable coronary syndromes
  - uncontrolled, unpredictable bleeding
  - impaired pulmonary function
  - increased O_2 consumption

Selection of Red Cells for Transfusion
- when anticipating an RBC transfusion, the following should be ordered:
  - group and screen: determines the blood group and Rh status of the recipient as well as the presence of autoantibodies vs. major/minor blood group antigens in the patient's serum
  - cross-match: involves mixing the recipient's blood with potential donor blood and looking for agglutination (takes 30-45 min)
- when blood is required, several options are available
  - 1st line: fully crossmatched blood, electronic crossmatch is becoming more widely used (not always available in emergency situations)
  - 2nd line: donor blood of the same group and Rh status as the recipient
  - 3rd line: O- blood for females of reproductive age; O+ blood for all others

1 unit of pRBC will increase Hb by approximately 10 g/L or increase Hct by 4%

American Society of Hematology Choosing Wisely Recommendation
Do not transfuse more than the minimum number of RBC units necessary to relieve symptoms of anemia or to return the patient to a safe hemoglobin range (70-80 g/L) in stable non-cardiac patients

Transfusion Requirements in Critical Care (TRICC)
NEJM 1999;340:409-417
Study: Multicentre, RCT.
Participants: 838 critically ill patients with euvolemia after initial treatment and hemoglobin less than 9 g/dL within 72 h of ICU admission.
Intervention: Patients receiving a transfusion followed either (1) a restrictive strategy (RS; n=418) in which red cells were transfused if hemoglobin was less than 7.0 g/dL and then maintained at 7 to 9 g/dL) or (2) a liberal strategy (LS; n=420) in which transfusions occurred when the hemoglobin was less than 10.0 g/dL and then maintained at 10 to 12 g/dL.
Primary Outcome: Mortality at 30 d and severity of organ dysfunction.
Results: Mortality rates at 30 d were similar between groups. However, mortality rates were significantly lower with the RS among less acutely ill patients (8.7% and RS group and 16.1% in LS group; p=0.03) and among those <55 yr of age (5.7% RS and 13% LS; p=0.02), but did not differ in a subgroup with clinically significant cardiac disease.
Conclusion: A RS of red cell transfusion is at least as effective as, and possibly superior to, a LS transfusion in critically ill patients.

Platelets

Table 37. Platelet Products

Product	Indication
Random donor (pooled)	Thrombocytopenia with bleeding
Single donor platelets	Potential BMT recipients
HLA matched platelets	Refractory to pooled or single donor platelets, presence of HLA antibodies

- stored at 20-24°C
- random donor platelets are transfused from a pool of 4 units; this should increase the platelet count by ≥15 x 10^9/L
- single donor platelets (transfused as single units) should increase the platelet count by 40-60 x 10^9/L
- if an increase in the platelet count is not seen post-transfusion: autoantibodies (i.e. ITP), alloantibodies, consumption (bleeding, sepsis), or hypersplenism may be present

Table 38. Indications for Platelet Transfusion

Plt (x 10^9/L)	Indications
<10	Non-immune thrombocytopenia
<20	Procedures not associated with significant blood loss
<50	Procedures associated with blood loss or major surgery (>500 mL EBL)
<100	Pre-neurosurgery or head trauma
Any	Platelet dysfunction (or antiplatelet agents) and marked bleeding

Relative Contraindications of Platelet Transfusion
- TTP, HIT, post-transfusion purpura, HELLP

Liberal or Restrictive Transfusion in High-Risk Patients After Hip Surgery (FOCUS)
NEJM 2011;365:2453-2462
Study: Multicentre RCT.
Participants: 2,016 patients aged greater than 50 yr with a history of or risk factors for cardiovascular disease and hemoglobin (Hb) level below 10 g/dL after hip-fracture surgery.
Intervention: Patients were randomly assigned to a liberal transfusion strategy (a Hb threshold of 10 g/dL) or a restrictive transfusion strategy (anemia symptoms or at physician discretion for a Hb level less than 8 g/dL).
Primary Outcome: Mortality or inability to walk across a room without human assistance on a 60 day follow-up.
Results: Primary outcome rates were 35.2% in the liberal transfusion strategy group and 34.7% in the restrictive transfusion strategy group. Rates of complications were similar in the two groups.
Conclusion: A liberal transfusion strategy did not reduce mortality rates or the inability to walk independently on 60 d follow-up compared to a restrictive transfusion strategy in elderly patients with high cardiovascular risk factors after hip surgery.

Coagulation Factors

Table 39. Coagulation Factor Products

Product	Indication
Frozen plasma (FP)	Depletion of multiple coagulation factors (e.g. sepsis, DIC, dilution, TTP/HUS, liver disease), emergency reversal of life-threatening bleeding secondary to warfarin overdose
Cryoprecipitate (enriched fibrinogen, vWF, VIII, XIII)	Factor VIII deficiency von Willebrand disease Hypofibrinogenemia
Hemate P	von Willebrand disease
Factor VIII concentrate	Factor VIII deficiency (Hemophilia A)
Factor IX concentrate	Factor IX deficiency (Hemophilia B)
Recombinant VIIa	Factor VII deficiency with bleeding, Hemophilia A or B with inhibitors
Prothrombin complex (Octaplex®)	Reversal of warfarin therapy or vitamin K deficiency in bleeding patient or in patient requiring urgent (<6 h) surgical procedure

Acute Blood Transfusion Reactions

IMMUNE

Acute Hemolytic Transfusion Reactions

- ABO incompatibility resulting in intravascular hemolysis secondary to complement activation, occurs immediately after transfusion
- most commonly due to incorrect patient identification
- risk per unit of blood is <1 in 40,000
- presentation: fever, chills, hypotension, back or flank pain, dyspnea, hemoglobinuria
- acute renal failure (<24 h) and DIC
- treatment
  - stop transfusion
  - notify blood bank and check for clerical error
  - maintain BP with vigorous IV fluids ± inotropes
  - maintain urine output with diuretics, crystalloids, dopamine

DDx of Post-Transfusion Fever
- Acute hemolytic transfusion reaction
- Febrile non-hemolytic transfusion reaction
- Bacterial contamination
- Allergy

DDx of Post-Transfusion Dyspnea
- Transfusion-associated circulatory overload (TACO)
- Transfusion-related acute lung injury (TRALI)
- Allergy (bronchospasm/anaphylaxis)

Febrile Nonhemolytic Transfusion Reactions

- due to alloantibodies to WBC, platelets or other donor plasma antigens, and release of cytokines from blood product cells
- occurs within 0-6 h of transfusion
- risk per unit of blood is 1 in 100 (minor), 1 in 10,000 to 40,000 (severe)
- presents with fever ± rigors, facial flushing, headache, myalgia, hypotension
- treatment
  - rule out hemolytic reaction or infection
  - if temperature <38°C, continue with transfusion but decrease rate and give antipyretics
  - if temperature >38°C, stop transfusion, give antipyretics and anti-histamine

Allergic Nonhemolytic Transfusion Reactions

- alloantibodies (IgE) to proteins in donor plasma result in mast cell activation and release of histamine
- occurs mainly in those with history of multiple transfusions or multiparous women
- risk per unit of blood is 1 in 100
- presents mainly as urticaria and occasionally with fever
- can present as anaphylactoid reaction with bronchospasm, laryngeal edema, and hypotension, but this occurs mainly in IgA deficient patients that have anti-IgA antibodies
- treatment
  - mild: slow transfusion rate and give diphenhydramine
  - moderate to severe: stop transfusion, give IV diphenydramine, steroids, epinephrine, IV fluids, and bronchodilators

Transfusion-Related Acute Lung Injury

- new-onset acute lung injury that occurs during transfusion or within 6 h of transfusion completion
  - insidious, acute onset of pulmonary insufficiency
  - profound hypoxemia (PaO_2/FiO_2 <300 mmHg)
  - bilateral pulmonary edema on CXR
  - pulmonary artery wedge pressure <18 mmHg
  - no clinical evidence of left atrial hypertension
- pathogenesis uncertain; perhaps due to binding of donor antibodies to WBC of recipient and release of mediators that increase capillary permeability in the lungs
- typically occurs 2-4 h post transfusion and resolves in 24-72 h
- risk per unit of blood is 1 in 10,000
  - is currently the leading cause of transfusion-related morbidity and mortality
- treatment: supportive therapy (oxygen)
- inform blood bank; patient and donor testing will be arranged

NONIMMUNE

Transfusion-Associated Circulatory Overload
- due to impaired cardiac function and/or excessive rapid transfusion
- presentation: dyspnea, orthopnea, hypotension, tachycardia, crackles at base of lung, and increased venous pressure
- incidence: 1 in 700 and is becoming more common
- treatment: transfuse at lower rate, give diuretics and oxygen

Bacterial Infection
- Gram positive: *S. aureus, S. epidermidis, Bacillus cereus*
- Gram negative: *Klebsiella, Serratia, Pseudomonas, Yersinia*
- overall risk is 1 in 100,000 for RBC and 1 in 10,000 for platelets
- never store blood >4 h after bag has left blood bank
- treatment: stop transfusion, blood cultures, IV antibiotics, fluids

Hyperkalemia
- due to K^+ release from stored RBC
- risk increases with storage time and if blood is irradiated and risk decreases if given fresh blood
- occurs in 5% of massively transfused patients
- treatment: see Nephrology, NP12

Citrate Toxicity
- occurs with massive transfusion in patients with liver disease – patients are unable to clear citrate from blood
- citrate binds to Ca^{2+} and causes signs and symptoms of hypocalcemia
- treatment: IV calcium gluconate (10 mL for every 2 units of blood)

Dilutional Coagulopathy
- occurs with massive transfusion (>10 units)
- pRBC contains no clotting factors, fibrinogen, cryoprecipitate, or platelets
- treatment: FP, cryoprecipitate, and platelets

Delayed Blood Transfusion Reactions

IMMUNE

Delayed Hemolytic
- due to alloantibodies to minor antigens such as Rh, Kell, Duffy, and Kidd
- level of antibody at time of transfusion is too low to cause hemolysis; later the level of antibody increases due to secondary stimulus and causes extravascular hemolysis
- occurs 5-7 d after transfusion
- presentation: anemia and mild jaundice
- treatment: no specific treatment required; important to note for future transfusion

Transfusion-Associated Graft Versus Host Disease
- transfused T-lymphocytes recognize and react against "host" (recipient)
- occurs 4-30 d following transfusion
- most patients already have severely impaired immune systems (e.g. Hodgkin lymphoma or leukemia)
- presentation: fever, diarrhea, liver function abnormalities, and pancytopenia
- can be prevented by giving irradiated blood products

NONIMMUNE

Iron Overload
- due to repeated transfusions over long period of time (e.g. β-thalassemia major)
- can cause secondary hemochromatosis
- treatment: iron chelators or phlebotomy if no longer requiring blood transfusion and not anemic

Viral Infection Risk
- HBV <1 in 153,000
- Human T-lymphotropic virus (HTLV) <1 in 4,300,000
- HCV <1 in 2,300,000
- HIV <1 in 7,000,000
- other infections include EBV, CMV, WNV (West Nile virus)

Common Medications

Antiplatelet Therapy

• see Figure 11a, *Platelet Activation Cascade*, H26

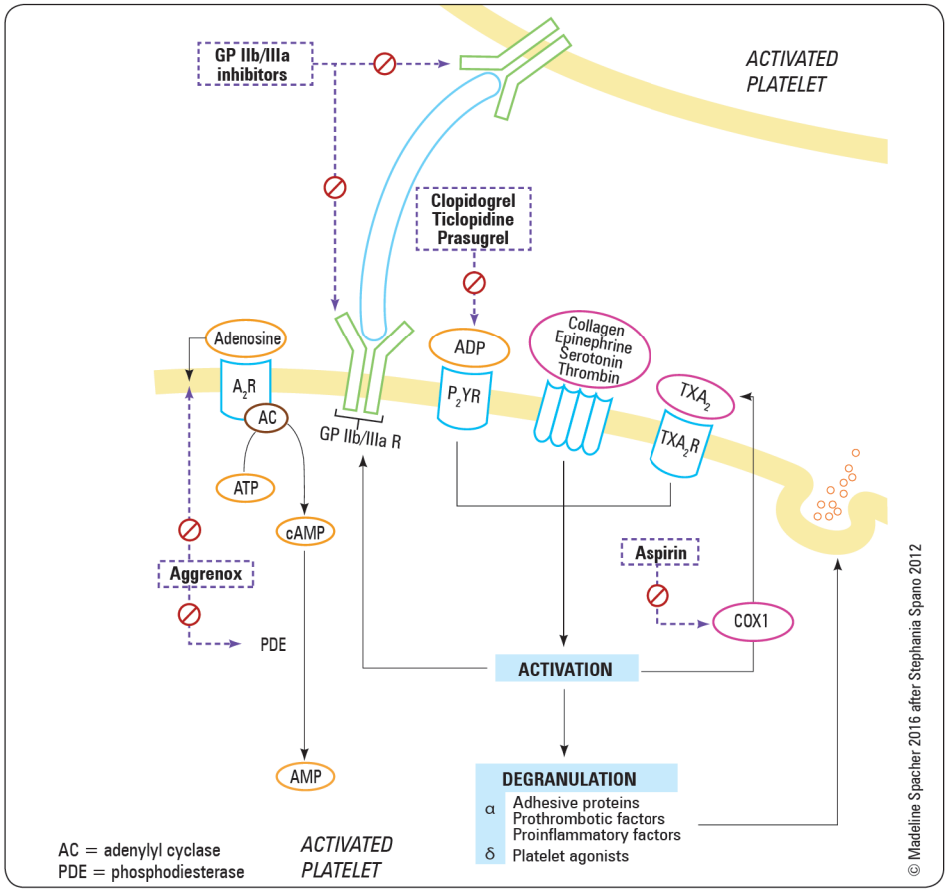


Figure 15. Mechanisms of action of antiplatelet therapy

Antiplatelet/Anticoagulation and Pregnancy

Class A
- None

Class B
- Argatroban
- Fondaparinux
- Clopidrogel
- LMWH

Class C
- ASA (1st and 2nd trimesters)
- Heparin
- Dabigatran
- Abciximab
- Rivaroxaban

Class D
- ASA (in 3rd trimester)
- Aggrenox
- Warfarin (warfarin embryopathy)

Class X
- Warfarin (warfarin embryopathy)

Table 40. Antiplatelet Therapy

	Mechanism of Action	Dose/Route of Administration	Onset/Peak/Duration	Specific Side Effects	Remarks
Aspirin® (ASA)	Irreversibly acetylates COX, inhibiting TXA2 synthesis, thus inhibiting platelet aggregation	Single loading 200-300 mg PO, followed by dose of 75-100 mg PO daily	Onset: 5-30 min Peak: 0.25-3 h Duration: 3-6 h	GI ulcer/bleeding Tinnitus Bronchospam Angioedema Reye's syndrome in pediatric patients	Indicated for stroke/MI prophylaxis Reduce incidence of recurrent MI Decrease mortality in post-MI patients Contraindicated in patients with GI ulcers
Aggrenox® (ASA + Dipyridamole)	Dipyridamole increases intracellular cAMP levels, which inhibits TXA2 synthesis, leading to decreased platelet aggregation	1 capsule PO bid	Peak: 75 min	H/A Dyspepsia N/V Abdominal pain Cardiac failure Hemorrhoids	More effective than ASA in secondary prevention of stroke Dipyridamole potentiates antiplatelet action of ASA
Clopidogrel (Plavix®)	Inhibit ADP binding to platelets, thus decreased platelet aggregation	75-300 mg PO daily	Onset: 2 h Peak: 1 h	URI Chest pain H/A Flu-like syndrome Depression UTI GI hemorrhage Pancytopenia May cause TTP	Prevention of cardiovascular events in high-risk patients CYP2C19 poor metabolizers have diminished response to clopidrogrel Caution with hepatic/renal impairment
Glycoprotein IIb/IIIa Inhibitors (Reopro® [abciximab], Integrelin® [epti])	Blocking GP II/IIIa receptor inhibits fibrinogen and vWF binding, leading to decreased platelet aggregation	Variable IV	Variable	Hypotension Back pain N/V Chest pain Abdominal pain Thrombocytopenia	Used most commonly in cardiac catheterization Contraindicated in PUD Monitoring aPTT/activated clotting time

Anticoagulant Therapy

Table 41. Anticoagulant Therapy

	Mechanism of Action	Dose/Route of Administration	Onset/Peak/ Duration	Reversing Agent	Monitoring	Specific Side Effects	Remarks
Heparin	Accelerates activity of antithrombin	As per hospital nomogram	Onset: 20-60 min Peak: 2-4 h	Protamine sulfate	aPTT (intrinsic pathway), UFH (anti-Xa) levels	Hemorrhage HIT Increased liver enzymes	Pregnancy: safe (does not cross placenta)
Warfarin	Vitamin K antagonist: inhibits production of II, VII, IX, X, proteins C and S	Individualized dosing by monitoring PT/INR PO	Onset: 36-48 h Peak: 1.5-3 d	IV vitamin K PCC FFP	PT/INR maintain 2-3 (2.5-3.5 for mechanical values)	Hemorrhage Cholesterol embolism syndrome Intraocular hemorrhage	Pregnancy: not used, can cross placenta (teratogenic)
LMWH (enoxaparin, dalteparin, tinzaparin)	Inhibits FXa	Variable SC/IV	Onset: 3-5 h Peak: 3-5 h Duration: 12 h	Partial reversibility with protamine sulfate	FXa in pediatrics, pregnancy and weight >150 kg	Hemorrhage Fever Increased liver enzymes <1% HIT	Increased bioavailability than heparin Can accumulate in patients low CrCl (<30)
Fondaparinux	Selective inhibitor of FXa	Variable SC daily	Onset: 2 h Peak: 2-3 h	Not reversible	None	Anemia Fever Nausea Rash	Heparin analogue Contraindicated in renal failure
Rivaroxaban	Anti-FXa	PO	Peak: 2-4 h	Not reversible	None	Syncope GI hemorrhage	Indicated in treatment of acute VTE (non-cancer patients), secondary VTE prevention, thromboprophylaxis in orthopedic patients and stroke prophylaxis in non-valvular AFib; ensure CrCl>30
Apixaban	Anti-FXa	PO	Onset: 3-4h Peak: 3-4 h	Not reversible	None	Hemorrhage Nausea Anemia	Indicated for stroke prophylaxis in non-valvular AFib; Idiopathic VTE; ensure CrCl >30
Argatroban	Direct thrombin inhibitor	Variable IV	Onset: 5-10 min Duration: 20-40 min	Not reversible	aPTT	Dyspnea Hypotension Fever	Indicated for HIT, renal failure, unstable patients
Dabigatran	Direct thrombin inhibitor	150 mg PO bid	Peak: 1 h	Not reversible	None (prolonged aPTT can suggest residual drug on board)	GI upset Dyspepsia	Only indicated for AFib in Canada Contraindicated in renal failure, cancer patients, mechanical heart valves

Adverse Reactions of Heparin

- hemorrhage: depends on dose, age, and concomitant use of antiplatelet agents or thrombolytics
- heparin-induced thrombocytopenia: associated with venous or arterial thrombosis (see Table 22, H29)
- osteoporosis: with long-term use

Low Molecular Weight Heparin (enoxaparin, dalteparin, tinzaparin)

- increased bioavailability compared to normal heparin
- increased duration of action
- SC route of administration
- do not need to monitor aPTT
- adverse reactions less common than UFH
- patients with renal failure (CrCl <30) can accumulate LMWH, therefore must adjust dose
- only partially reversible with protamine sulfate

Table 42. Recommended Therapeutic INR Ranges of Common Indications for Oral Anticoagulant Therapy

Indication	INR Range
Prophylaxis of venous thrombosis (high-risk surgery) Treatment of venous thrombosis Most cases of thrombosis with antiphospholipid antibody syndrome Treatment of pulmonary embolism Prevention of systemic embolism Tissue heart valves AMI (to prevent systemic embolism) Valvular heart disease Atrial fibrillation Bileaflet mechanical valve in aortic position	2.0-3.0
Mechanical prosthetic mitral valves (high risk) Prophylaxis of recurrent myocardial infarction	2.5-3.5

AMI = acute myocardial infarction

Dabigatran vs. Warfarin in Patients with Atrial Fibrillation
NEJM 2009;361:1139-1151
Study: Non-inferiority trial with 2 yr follow-up.
Methods: Random assignment of 18,113 patients with atrial fibrillation and risk of stroke to fixed doses of dabigatran (blinded, 110 mg or 150 mg bid) or adjusted-dose warfarin (unblinded). Primary outcome was stroke or systemic embolism.
Results: The warfarin, dabigatran 110 mg, and dabigatran 150 mg groups showed the following rates: 1) stroke or systemic embolism was 1.69%, 1.53%, and 1.11% per year respectively, 2) major bleeding was 3.36%, 2.71%, and 3.11% per year respectively, 3) hemorrhagic stroke was 0.38%, 0.12%, and 0.10% per year respectively ($p<0.001$), 4) mortality was 4.13%, 3.75%, and 3.64% respectively.
Conclusions: In patients with atrial fibrillation, dabigatran 110 mg was similar to warfarin in rates of stroke and systemic embolism but had lower rates of major hemorrhage. Dabigatran 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.

Table 43. Recommended Management of a Supratherapeutic INR

INR	Bleeding Present	Recommended Action
>Therapeutic to 4.5	No	Lower warfarin dose **OR** Omit a dose and resume warfarin at a lower dose when INR is in therapeutic range **OR** No dose reduction needed if INR is minimally prolonged
>4.5 to 10.0	No	Omit the next 1 to 2 doses of warfarin, monitor INR more frequently and resume treatment at a lower dose when INR is in therapeutic range **OR** Omit a dose and administer 1 to 2.5 mg oral vit K in patients with increased risk of bleeding
>10.0	No	Hold warfarin and administer 5 to 10 mg oral vit K; monitor INR more frequently and administer more vit K as needed; resume warfarin at a lower dose when INR is in therapeutic range
Any	Serious or life threatening	Hold warfarin and administer 10 mg vit K by slow IV infusion; supplement with four-factor prothrombin complex concentrate; monitor and repeat as needed

Adapted from:. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;(2 suppl):e152S

Chemotherapeutic and Biologic Agents Used in Oncology

Table 44. Selected Chemotherapeutic and Biologic Agents

Class	Example	Mechanism of Action or Target
Alkylating Agent	• chlorambucil, cyclophosphamide, melphalan (nitrogen mustards) • carboplatin, cisplatin • dacarbazine, procarbazine • busulfan • bendamustine	Damage DNA via alkylation of base pairs Leads to cross-linking of bases, abnormal base-pairing, DNA breakage
Antimetabolites	• methotrexate (folic acid antagonist) • 6-mercaptopurine, fludarabine (purine antagonist) • 5-fluorouracil (5-FU) (pyrimidine antagonist) • hydroxyurea • cytarabine	Inhibit DNA synthesis
Antibiotics	• adriamycin (anthracycline) • bleomycin • mitomycin C • daunorubicin	Interfere with DNA and RNA synthesis
Taxanes	• paclitaxel • docetaxel	Stabilize microtubules against breakdown once cell division complete
Vinca-alkaloids	• vinblastine • vincristine • vinorelbine	Inhibit microtubule assembly (mitotic spindles), blocking cell division
Topoisomerase Inhibitors	• irinotecan, topotecan (topo I) • etoposide (topo II)	Interfere with DNA unwinding necessary for normal replication and transcription
Steroids	• prednisone • dexamethasone	Immunosuppression
Purine Analogues	• fludarabine • cladribine	Interferes with DNA synthesis
Monoclonal Antibodies	• trastuzumab (Herceptin®) • bevacizumab (Avastin®) • rituximab (Rituxan®), ofatumumab (Arzerra®), obinutuzumab (Gayzva®) • cetuximab (Erbitux®)	HER2 antagonist VEGF antagonist CD20 antagonist EGFR antagonist
Small Molecule Inhibitors	• imatinib mesylate (Gleevec®) • dasatinib • nilotinib • erlotinib (Tarceva®) • gefitinib (Iressa®) • bortezomib (Velcade®) • sunitinib (Sutent®) • ibrutinib (Imbruvica®) • idealasib (Zyedlig®) • ruxolitinib (Jakavi®)	*Bcr-Abl* inhibitor *Bcr-Abl* inhibitor *Bcr-Abl* inhibitor EGFR antagonist EGFR antagonist 26S proteasome inhibitor VEGFR, PDGFR antagonist BTK inhibitor P13K inhibitor JAK2 inhibitor

Landmark Hematology Trials

Trial	Reference	Results
Hematologic Malignancies and Related Disorders		
Hodgkin Lymphoma: ABVD vs. MOPP	*NEJM* 1992; 327:1478-84	In Hodgkin lymphoma, ABVD regimen has equal failure-free and overall survival to MOPP + ABVD, but less myelotoxicity; ABVD is standard chemotherapy for Hodgkin lymphoma
CHOP	*NEJM* 1993; 328:1002-6	In NHL, CHOP has lowest incidence of fatal toxic reactions and shows no significant difference from 3 other regimens in response or disease-free/overall survival; CHOP is the standard for advanced NHL
R-CHOP	*NEJM* 2002; 346:235-42	Addition of rituximab to CHOP increases complete response rate and prolongs event-free survival and overall survival in elderly with DLBCL
CML: Imatinib vs. IFN + Cytarabine	*NEJM* 2003; 348:994-1004	In patients with chronic-phase CML, imatinib was more effective than IFNα + cytarabine in inducing cytogenetic response and freedom from progression to accelerated phase/blast crisis
AZA-001	*Lancet Oncol* 2009; 10:223-32	Azacitidine increases overall survival in higher-risk myelodysplastic syndrome than conventional care
CLL8	*Lancet* 2010; 376:1164-74	Rituximab plus fludarabine and cyclophosphamide (FCR) improves progression-free and overall survival compared with fludarabine and cyclophosphamide alone (FC) in the treatment of CLL
VISTA	*JCO* 2010; 28:2259-66	Bortezomib plus melphalan and prednisone (MPV) is superior to melphalan and prednisone (MP) in overall survival of non-transplant-eligible multiple myeloma patients
MInT Group	*Lancet* 2011; 12:1013-1022	Rituximab added to CHOP-like chemotherapy improved long-term outcomes for young patients with good-prognosis DLBCL
CYTO-PV	*NEJM* 2013; 368(1), 22-33	In patients with polycythemia vera, a hematocrit target of <0.45 for cytoreductive therapy is associated with prevention of thromobotic complications
StIL	*Lancet* 2013; 381(9873):1203-10	Bendamustine plus rituximab is superior to R-CHOP in terms of progression-free survival and fewer toxic effects in patients with previously untreated indolent lymphoma
Ibrutinib vs. Ofatumumab in previously treated CLL	*NEJM* 2014; 371:213-223	Ibrutinib, as compared with ofatumumab, significantly improved progression-free survival, overall survival, and response rate among patients with previously treated CLL or SLL
Trombosis		
CLOT	*NEJM* 2003; 349:146-53	In patients with cancer and acute venous thromboembolism, LWMH was more effective than warfarin in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding
PT1	*NEJM* 2005; 353:85-6	Hydroxyurea plus low-dose ASA is superior to anagrelide plus low-dose ASA for patients with essential thrombocythemia at high risk for vascular events
ESPIRIT	*Lancet* 2006; 367:1665-73	ASA plus dipyridamole is recommended over ASA alone as antithrombotic therapy after cerebral ischemia of arterial origin
Dabigatran vs. Warfarin in VTE	*NEJM* 2009; 361:2342-52	In the treatment of venous thromboembolism, dabigatran is as effective as warfarin and also has a similar safety profile; note: many problems in the trial, making it less pivotal in having drug approval
EINSTEIN-PE	*NEJM* 2012; 366: 1287-1297	Among patients with acute PE, rivaroxaban is noninferior to warfarin in preventing recurrent VTE, and is associated with similar bleeding rates
AMPLIFY	*NEJM* 2013: 369: 799-808	In patients with VTE who have completed 6-12 months of anticoagulation, long-term apixaban treatment reduces recurrent VTE or all-cause mortality without increasing rates of major bleeding.
Blood Products and Transfusion		
Platelet Transfusion Threshold	*NEJM* 1997; 337:1870-5	The risk of major bleeding in patients with AML undergoing induction chemotherapy was similar whether the platelet-transfusion threshold was set at 20 or 10; use of the lower threshold reduced platelet usage by 21.5%
TRICC BP	*NEJM* 1999; 340:409-17	A restrictive strategy of red-cell transfusion (when Hb <70) is at least as effective as and possibly superior to a liberal transfusion strategy (when Hb <100) in ICU patients; one possible exception is patients with an acute MI or unstable angina
Dose of Platelet Transfusion	*NEJM* 2010; 362:600-13	Low dose prophylactic platelet transfusion decreases total number of platelets transfused but increases number of transfusions but not incidence of bleeding in patients with hypoproliferative thrombocytopenia
Transfusion in High-Risk Patients after Hip Surgery	*NEJM* 2011; 365:2453-2462	A liberal transfusion strategy (Hb <100), as compared with a restrictive strategy (anemia symptoms or at physician discretion for Hb<80), did not reduce rates of death or inability to walk independently on 60-day follow-up or reduce in-hospital morbidity in elderly patients at high cardiovascular risk
Therapeutic Platelet Transfusion	*Lancet* 2012; 380:1309-16	Therapeutic platelet transfusions (when bleeding occurs) may be used if severe bleeding can be identified early in autologous stem-cell transplant patients; prophylactic transfusion (when platelets <10) should remain standard of care in AML patients
Transfusion Strategies for Acute Upper GI Bleeding	*NEJM* 2013; 368:11-21	As compared with a liberal transfusion strategy (Hb <90), a restrictive strategy (Hb<70) significantly improved outcomes in patients with acute upper gastrointestinal bleeding
Other		
MSH	*NEJM* 1995; 332:1317-22	Hydroxyurea is effective in reduction of complications and clinical manifestations of sickle cell disease
ITP: Dexamethasone	*NEJM* 2003; 349:831-6	A four-day course of high-dose dexamethasone is effective initial therapy for adults with immune thrombocytopenic purpura
CRASH-2	*Health Technol Assess* 2013; 17(10): 1-79	Early administration of TXA safely reduced the risk of death in bleeding trauma patients and is highly cost-effective. Treatment beyond 3 hours of injury is unlikely to be effective

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