CLINICAL HAEMATOLOGY

TAILORED FOR MEDICAL STUDENTS, USMLE, PLAB, PA & NURSING

4th EDITION

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PDF

107 PAGES

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What's included: Ready-to-study anatomy, physiology and pathology notes of the **Haematological (Hematological) 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.

Anatomy & Physiology Notes:

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- THE ROLE OF BLOOD IN THE IMMUNE SYSTEM
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BLOOD: AN OVERVIEW

BLOOD: AN OVERVIEW

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An Introduction To Blood:

- The main transport medium of the body
- 8% of body weight
- A special type of *Connective Tissue* (living cells suspended in a non-living matrix)
- More dense than water
- 5x more viscous than water
- pH between 7.35 & 7.45
- 37.4 degrees Celsius
- Average adult blood volume = 5L (women); 5.5L (men)

Blood Functions:

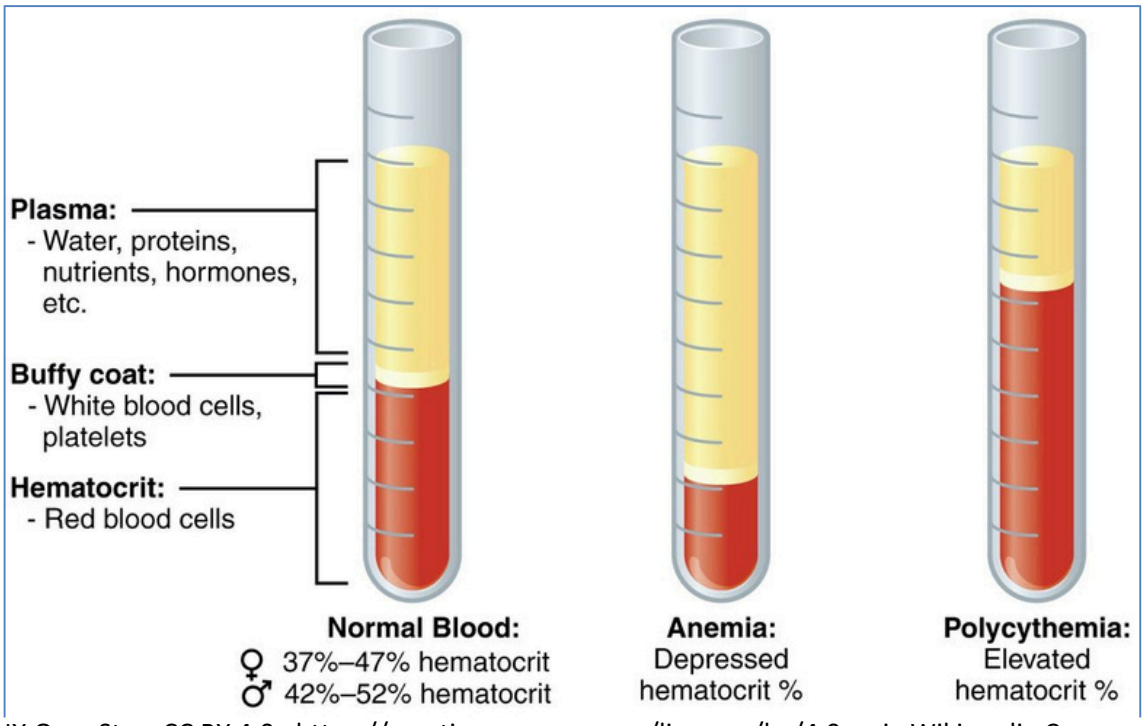
- **Distribution:**
  - Oxygen
  - Metabolic Waste
  - Hormones
- **Regulation:**
  - Temperature
  - Maintaining pH in body tissues
  - Fluid volume in Circulatory System
- **Protection:**
  - Preventing blood loss – clotting
  - Preventing infection

Major Blood Components:

Component and % of blood	Subcomponent and % of component	Type and % (where appropriate)	Site of production	Major function(s)
Plasma 46–63 percent	Water 92 percent	Fluid	Absorbed by intestinal tract or produced by metabolism	Transport medium
	Plasma proteins 7 percent	Albumin 54–60 percent	Liver	Maintain osmotic concentration, transport lipid molecules
		Globulins 35–38 percent	Alpha globulins—liver	Transport, maintain osmotic concentration
			Beta globulins—liver	Transport, maintain osmotic concentration
			Gamma globulins (immunoglobulins)—plasma cells	Immune responses
		Fibrinogen 4–7 percent	Liver	Blood clotting in hemostasis
	Regulatory proteins <1 percent	Hormones and enzymes	Various sources	Regulate various body functions
	Other solutes 1 percent	Nutrients, gases, and wastes	Absorbed by intestinal tract, exchanged in respiratory system, or produced by cells	Numerous and varied
Formed elements 37–54 percent	Erythrocytes 99 percent	Erythrocytes	Red bone marrow	Transport gases, primarily oxygen and some carbon dioxide
	Leukocytes <1 percent Platelets <1 percent	Granular leukocytes: neutrophils eosinophils basophils	Red bone marrow	Nonspecific immunity
		Agranular leukocytes: lymphocytes monocytes	Lymphocytes: bone marrow and lymphatic tissue	Lymphocytes: specific immunity
			Monocytes: red bone marrow	Monocytes: nonspecific immunity
	Platelets <1 percent		Megakaryocytes: red bone marrow	Hemostasis

Blood Components:

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



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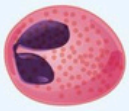
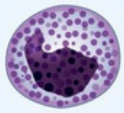
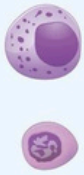
- **P la sm a :**
  - o Mostly water (90%)
  - o Contains 100's of dissolved nutrients/gases/hormones/wastes/ions/protein
  - o 5-7% protein:
    - § Albumin – blood carrier
    - § Globulin – mainly immunoglobulins
    - § Fibrinogen – part of a clotting protein
  - o Predominant Ions: Na+, K+, Ca2+, Mg2+, Cl-, HCO3-
- **Serum :**
  - o The fluid, noncellular portion of blood that remains after coagulation; lymphatic fluid
  - o Serum is equivalent to plasma without its clotting elements
- **Cells:**
  - o **Red Blood Cells**: AKA: Erythrocytes - carry oxygen around the body
  - o **White Blood Cells:** AKA: Leukocytes: (leuko = white)
    - § **Granulocytes:** (due to cytoplasmic granules)[are *polymorphonuclear* – Multilobed Nucleus]
      - **60% Neutrophils** - 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:
        - o Replenish resident macrophages and dendritic cells under normal states
      - **30% Lymphocytes** - Constantly circulating -Responsible for innate immune response (T-cells, B-cells & NK-cells)
        - o **T-Lymphocytes:** Responsible for *Cell-Mediated* immune response
        - o **B-Lymphocytes:** Responsible for *Humoral* immune response by producing antibodies
  - o **Platelets:** From fragmented Megakaryocytes – Responsible for Clotting

Formed element	Major subtypes	Numbers present per microliter (μL) and mean (range)	Appearance in a standard blood smear	Summary of functions	Comments
Erythrocytes (red blood cells)		5.2 million (4.4–6.0 million)	Flattened biconcave disk; no nucleus; pale red color	Transport oxygen and some carbon dioxide between tissues and lungs	Lifespan of approximately 120 days
Leukocytes (white blood cells)		7000 (5000–10,000)	Obvious dark-staining nucleus	All function in body defenses	Exit capillaries and move into tissues; lifespan of usually a few hours or days
	Granulocytes including neutrophils, eosinophils, and basophils	4360 (1800–9950)	Abundant granules in cytoplasm; nucleus normally lobed	Nonspecific (innate) resistance to disease	Classified according to membrane-bound granules in cytoplasm
	Neutrophils 	4150 (1800–7300)	Nuclear lobes increase with age; pale lilac granules	Phagocytic; particularly effective against bacteria. Release cytotoxic chemicals from granules	Most common leukocyte; lifespan of minutes to days
	Eosinophils 	165 (0–700)	Nucleus generally two-lobed; bright red-orange granules	Phagocytic cells; particularly effective with antigen- antibody complexes. Release antihistamines. Increase in allergies and parasitic infections	Lifespan of minutes to days
	Basophils 	44 (0–150)	Nucleus generally two-lobed but difficult to see due to presence of heavy, dense, dark purple granules	Promotes inflammation	Least common leukocyte; lifespan unknown
	Agranulocytes including lymphocytes and monocytes	2640 (1700–4950)	Lack abundant granules in cytoplasm; have a simple-shaped nucleus that may be indented	Body defenses	Group consists of two major cell types from different lineages
	Lymphocytes 	2185 (1500–4000)	Spherical cells with a single often large nucleus occupying much of the cell's volume; stains purple; seen in large (natural killer cells) and small (B and T cells) variants	Primarily specific (adaptive) immunity: T cells directly attack other cells (cellular immunity); B cells release antibodies (humoral immunity); natural killer cells are similar to T cells but nonspecific	Initial cells originate in bone marrow, but secondary production occurs in lymphatic tissue; several distinct subtypes; memory cells form after exposure to a pathogen and rapidly increase responses to subsequent exposure; lifespan of many years
	Monocytes 	455 (200–950)	Largest leukocyte with an indented or horseshoe-shaped nucleus	Very effective phagocytic cells engulfing pathogens or worn out cells; also serve as antigen-presenting cells (APCs) for other components of the immune system	Produced in red bone marrow; referred to as macrophages after leaving circulation
Platelets 		350,000 (150,000–500,000)	Cellular fragments surrounded by a plasma membrane and containing granules; purple stain	Hemostasis plus release growth factors for repair and healing of tissue	Formed from megakaryocytes that remain in the red bone marrow and shed platelets into circulation

HAEMATOPOIESIS

HAEMATOPOIESIS

(Yes, we know some countries spell it 'Hematopoiesis' :P)

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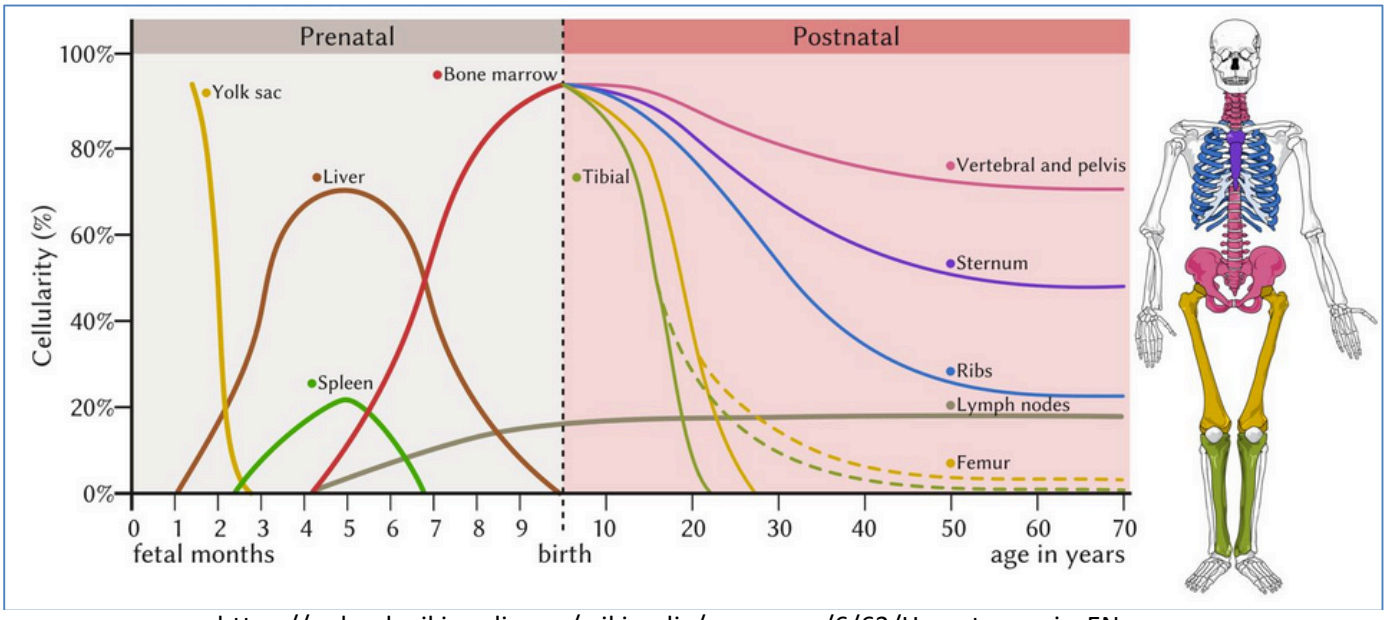
Haematopoiesis:

- **What is it?**
  - = 'The Formation of Cells in the Blood from ***Pluri-Potent Stem Cells***'
- **Why is it important?**
  - Blood cells don't live forever
  - Blood cells get used up/killed/broken down/sacrificed constantly
  - The body needs a way to balance this blood cell turnover with new production
  - Also need to be able to produce MORE of a CERTAIN blood cell type under different physiological conditions:
    - § Eg: High altitude hypoxia → Relative polycythemia
    - § Eg: Bacterial Infection → Neutrophilia
    - § Eg: Parasitic Infection → Eosinophilia
- **Where does it occur?**
  - **In Foetal Life:** Takes place in the Yolk Sac/Liver/Spleen/&Bone Marrow
  - **After Birth:** Takes place only in the **Bone Marrow** (Medullary Cavity)
    - § Ie: The Bone Marrow is generally the only source of *new blood cells*
    - § Usually confined to axial skeleton (pelvis & spine) & long bones (Femur & Humerus)
    - § However, the remaining *Fatty Marrow*, *Liver & Spleen* can resume their "extramedullary haematopoietic" roles in *Times of Need*



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ALL Blood Cells Start As Haematopoietic Stem Cells:

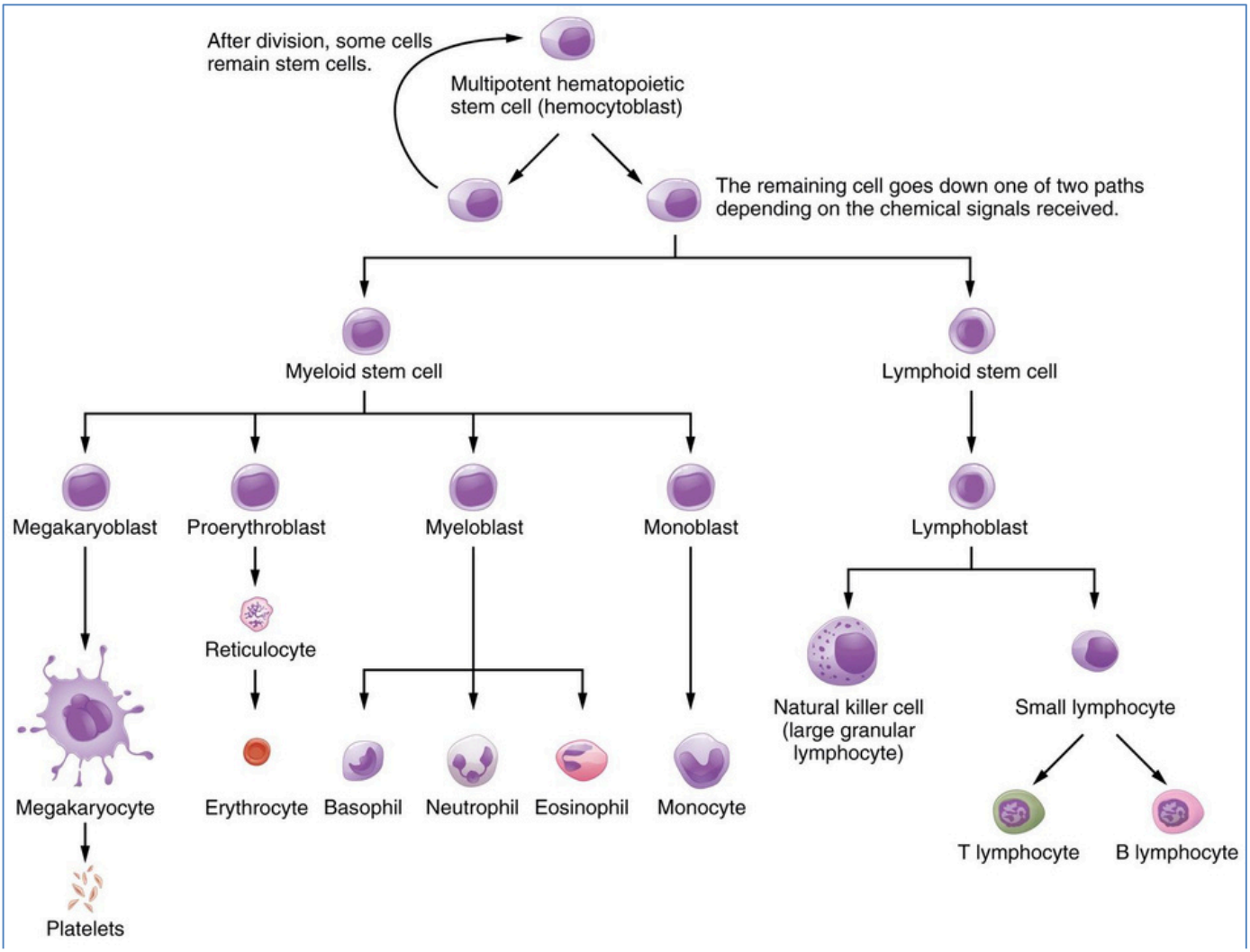
- Haematopoiesis starts with ***PluriPotent Stem Cells*** in the bone marrow
- Stem Cells are Self-renewing
- **Cell Lineages:**
    - o **Myeloid Stem Cells:**
        - § **Erythroid:**
        - § • Proerythroblast → Reticulocyte → **RBCs**

          Granulocytic:
            - Myeloblasts → **Neutrophils**
            - Eosinophilic Myeloblast → **Eosinophils**
            - Basophilic Myeloblast → **Basophils**
        - § **Monocytic:**
        - § • Monoblast → **Macrophages**

          Megakaryocytic:
            - Megakaryoblasts → Megakaryocytes → **Platelets**
    - o **Lymphoid Stem Cells:**
        - § **Lymphocytic:**
            - B-Lymphoblasts → **B-Cells**
            - T-Lymphoblasts → **T-Cells**
            - NK Cells
- **Considerable amplification**:
- o Ie: 1 Stem Cell can produce 10,000,000 blood cells after only 20 divisions

Leukemias & Lymphomas can result from defective haematopoietic stem cell lines;

- o Sometimes treated with total body irradiation to kill all defective stem cell lineages, → Then replace/regenerate the stem cell pool with a bone marrow transplant

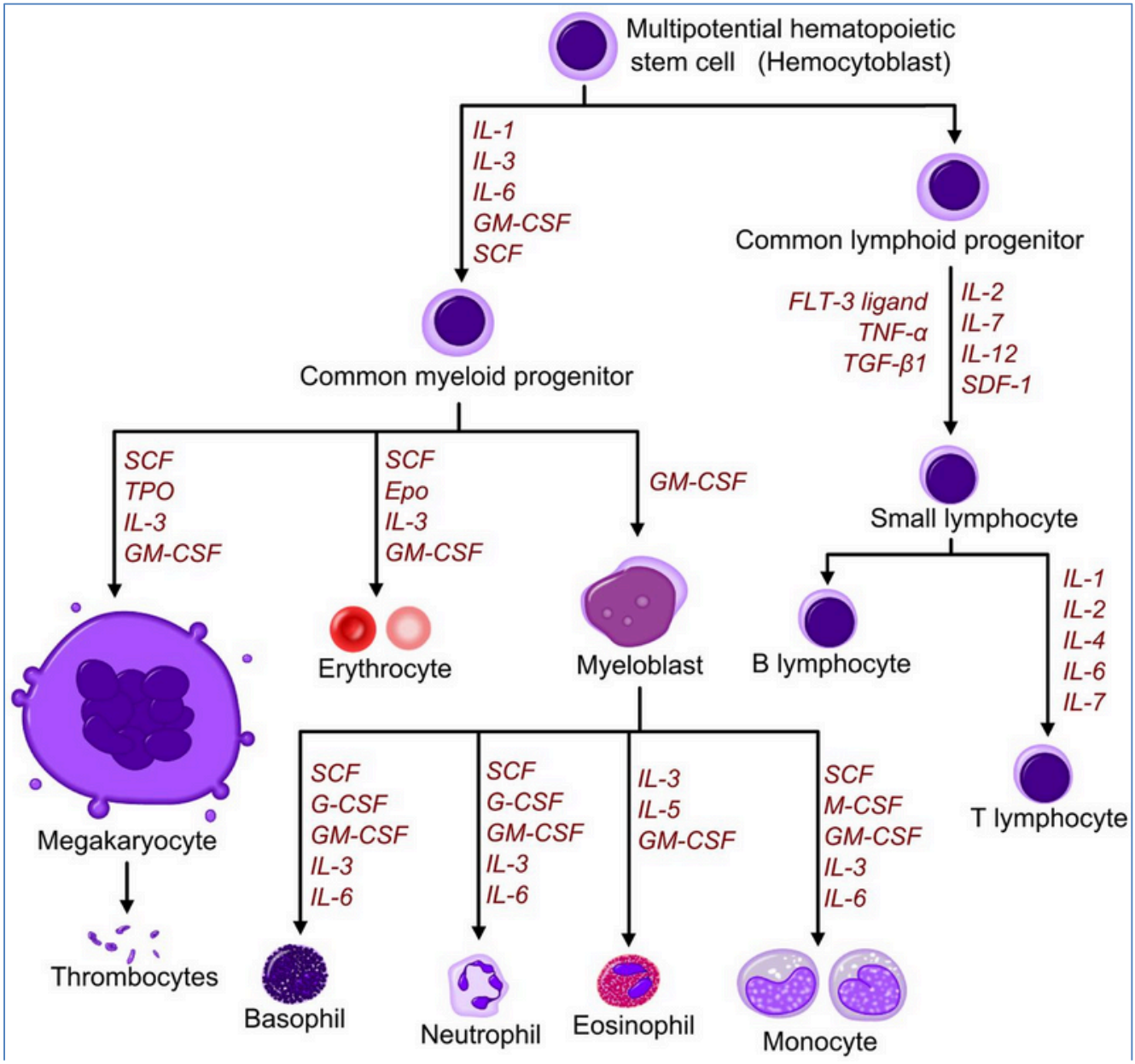


Haematopoietic Growth Factors:

- **Pluripotent Stem Cells are capable of becoming any type of cell**
- **Therefore, they need certain growth factors to direct their differentiation**
  - o Eg: Various Interleukins (IL's)
  - o Eg: Colony Stimulating Factors (CSF's)
  - o Eg: Thrombopoietin (TPO)
  - o Eg: Erythropoetin (EPO)
- **There are many growth factors, and unlimited combinations which could direct differentiation**
- o (Generally, committing these combinations to memory is outside the scope of a medical student)

Functions of these Growth Factors:

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



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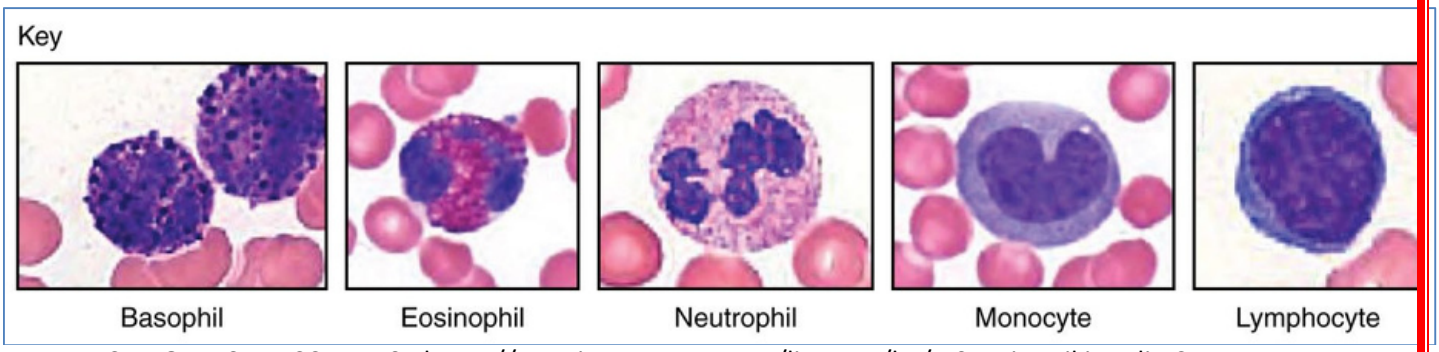
Normal Blood Smears:

- **RBCs:**
  - Most of the RBCs are round, have central pallor (due to being thinner at their centre)
  - RBC's size is comparable to a small lymphocyte
- **Other Cells:**
  - Neutrophils
  - Basophils
  - Eosinophils
  - Lymphocytes
  - Monocytes/Macrophages (Monocytes in Blood, Macrophages in Tissues)
  - Platelets



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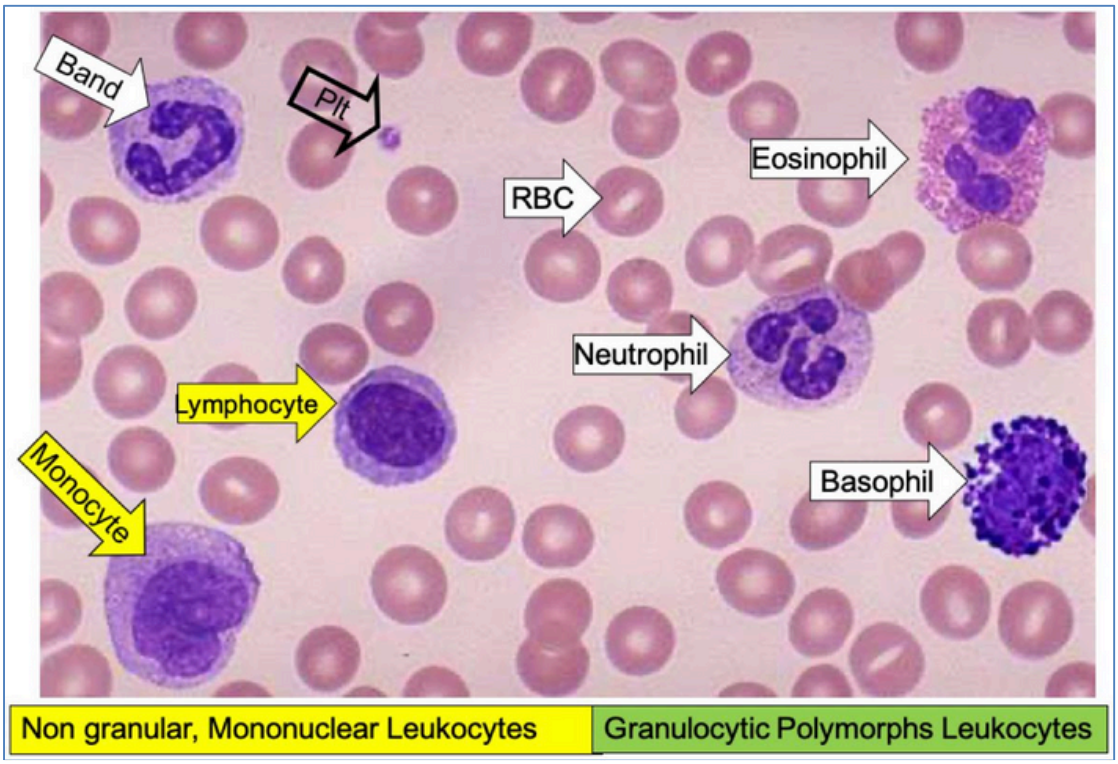
System for Looking at Blood Sm ears:

- (Usually performed by specialist pathologists; not general medical practitioners)
- **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:**
  - o **(Note: Philia = Too Many)**
  - o **(Note: Penia = Too Few)**

Cell Type	Causes of -Philias	Causes of –Penias
Neutrophils	Infection (bacterial, fungal) Trauma (surgery, burns) Infarction (MI, PE, Sickle-cell crisis) Inflammation (Gout, Rheum-Arthritis, IBD) Malignancy (Tumours, Hodgkin's disease) Myeloproliferative disease (Polycythaemia, CML) Physiological (Exercise, Pregnancy) Allergy (hay fever, asthma, eczema)	Infection (Viral, Salmonella, Malaria) Certain Drugs Autoimmune (Connective Tissue Disease) Alcohol Congenital (Kostmann's syndrome)
Eosinophils	Infection (Helminths, Viral) Skin disease Connective tissue disease (Polyarteritis Nodosa) Malignancy (Solid tumours, lymphomas) Drugs (gold) Myeloproliferative disease (Polycythaemia, CML)	Acute inflammation Drugs (steroids, Catecholamines)
Basophils	Inflammation (acute hypersensitivity, IBD) Iron Deficiency Infection (TB)	Hyperthyroidism
Monocytes	Inflammation (Connective tissue disease, IBD) Malignancy (Solid tumours)	
Lymphocytes	Infection (Viral, Bordetella Pertussis) Lymphoproliferative disease (CML, Lymphoma) Post-splenectomy	Inflammation (Connective tissue disease) Lymphoma Renal failure Drugs (Steroids, Cytotoxics) Congenital (Severe combined immunodeficiency)

RED BLOOD CELLS

RED BLOOD CELLS

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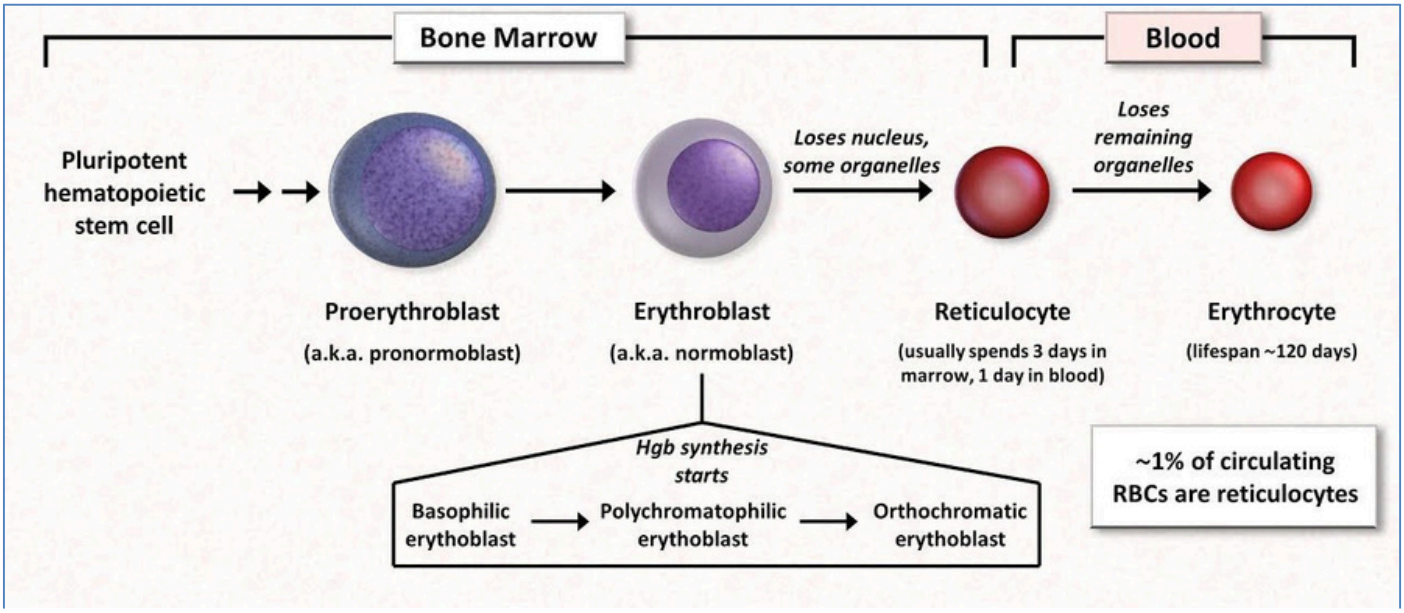
ERYTHROPOIESIS:

- **Erythropoiesis** = Process of **Red Blood Cell** Formation
  - Responsible for 1012 new erythrocytes each day
  - Finely Regulated
- **A similar sequence of *Amplification* & *Maturation***
  - **Pluripotent Stem Cells** → Pronormoblast (aka: Proerythroblast)
  - **Pronormoblasts** → progressively smaller Normoblasts (aka: Erythroblasts)
  - **Normoblasts** → Reticulocytes
  - **Reticulocytes** → Mature into Erythrocytes
  - Reticulocytes circulate in peripheral blood (1-2 days) before maturing in the *Spleen*
- **Presence of Nuclei/Organelles:**
  - As erythrocyte precursors mature, they ***gain haemoglobin*** & ***lose nuclear material***
  - **"Blasts"** = *Large, Nucleated RBC Progenitors + Organelles*
  - **"Reticulocytes"** = *Smaller, Non-Nucleated RBC Progenitors (No organelles; just remnants)*
- **Note: Presence of *Blasts* & *Reticulocytes* in *Peripheral Blood* means ↑↑Erythropoiesis:**
  - In a normal smear, less than 1% of RBCs are Reticulocytes
  - **Ie:** NORMALLY, All progenitors are in the marrow ONLY, except for the Erythrocyte
  - To view *Reticulocytes*, you need "*Methylene Blue Stain*"
  - Excess Reticulocytes can indicate Anaemia (Ie: The body's effort to compensate for lack of O2)
  - Severe Anaemia can result in immature nucleated RBC's in the blood (not good)



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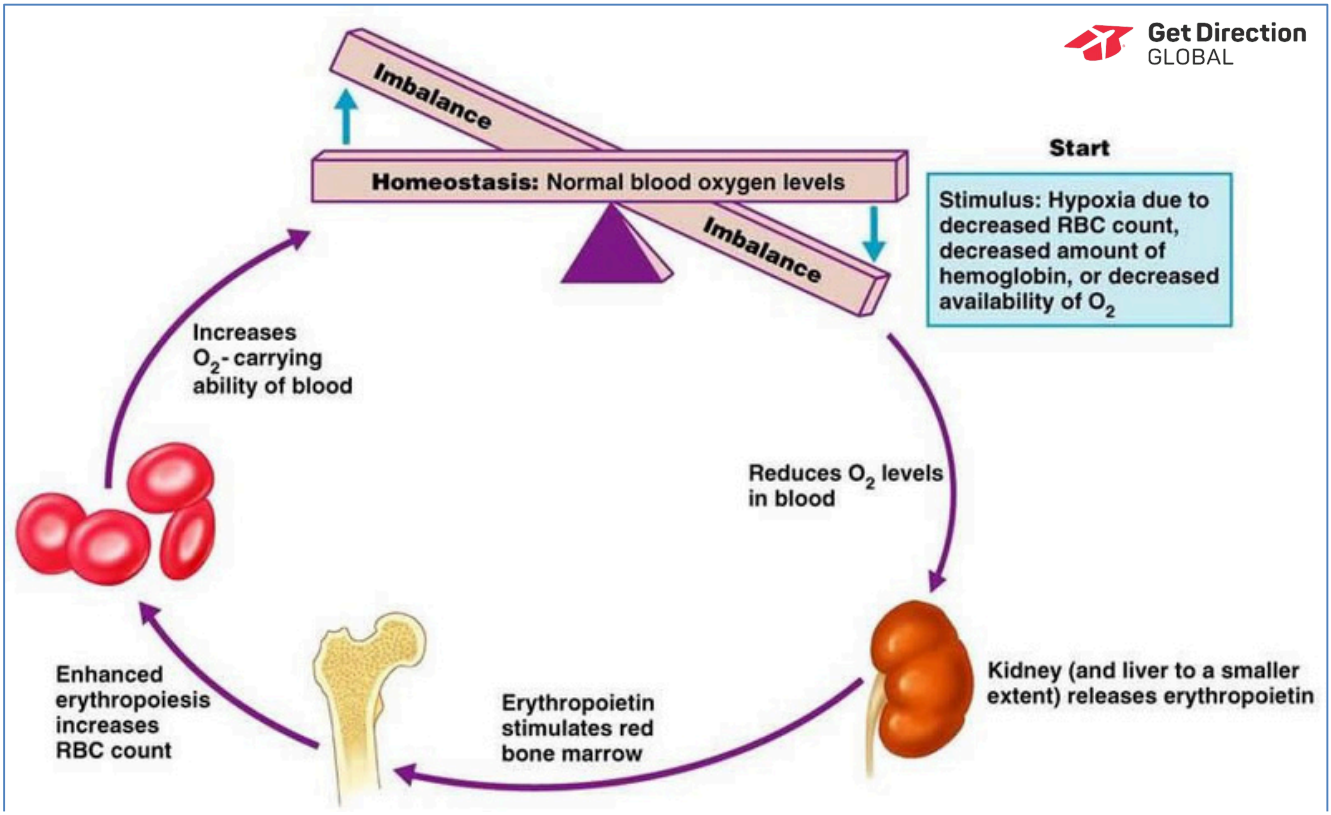
ERYTHROPOIETIN:

- 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 O2 normally (Eg: Carbon Monoxide Poisoning)
    - Atmospheric [O2] is low
    - Damage to Renal Circulation (Ie: Ischemia of Kidney)
  - **Production DECREASES when:**
    - Tissue Oxygenation is Normal



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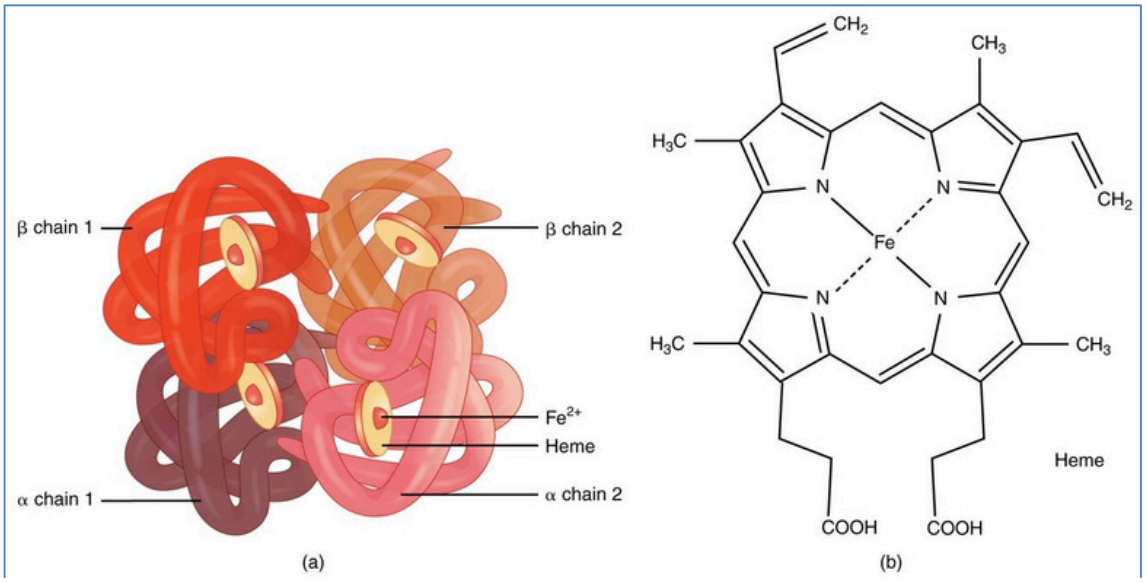
Requirements for Erythropoiesis & Haemoglobin Formation:

- **The *Marrow* requires other precursors for effective erythropoiesis: Eg:**
  - o **Metals:**
    - § Iron – essential for Haemoglobin synthesis
    - § Cobalt
  - o **Vitamins:**
    - § Especially Vit-B12 - necessary for normal DNA synthesis
    - § Folate - necessary for normal DNA synthesis
    - § Vit-C
    - § Vit-E
    - § Vit-B6
    - § Thiamine
    - § Riboflavin
    - § Pantothenic Acid
  - o **Amino Acids:**
    - § For the production of cell proteins
  - o **Hormones:**
    - § ***Erythropoietin***
    - § Androgens
    - § Thyroxine
    - § Interleukin-3
    - § GM-CSF (Granulocyte & Macrophage – Colony Stimulating Factor)

HAEMOGLOBIN:

- **Functions:**
  - To carry O2 to tissues
  - To Return CO2 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 **Haem *(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



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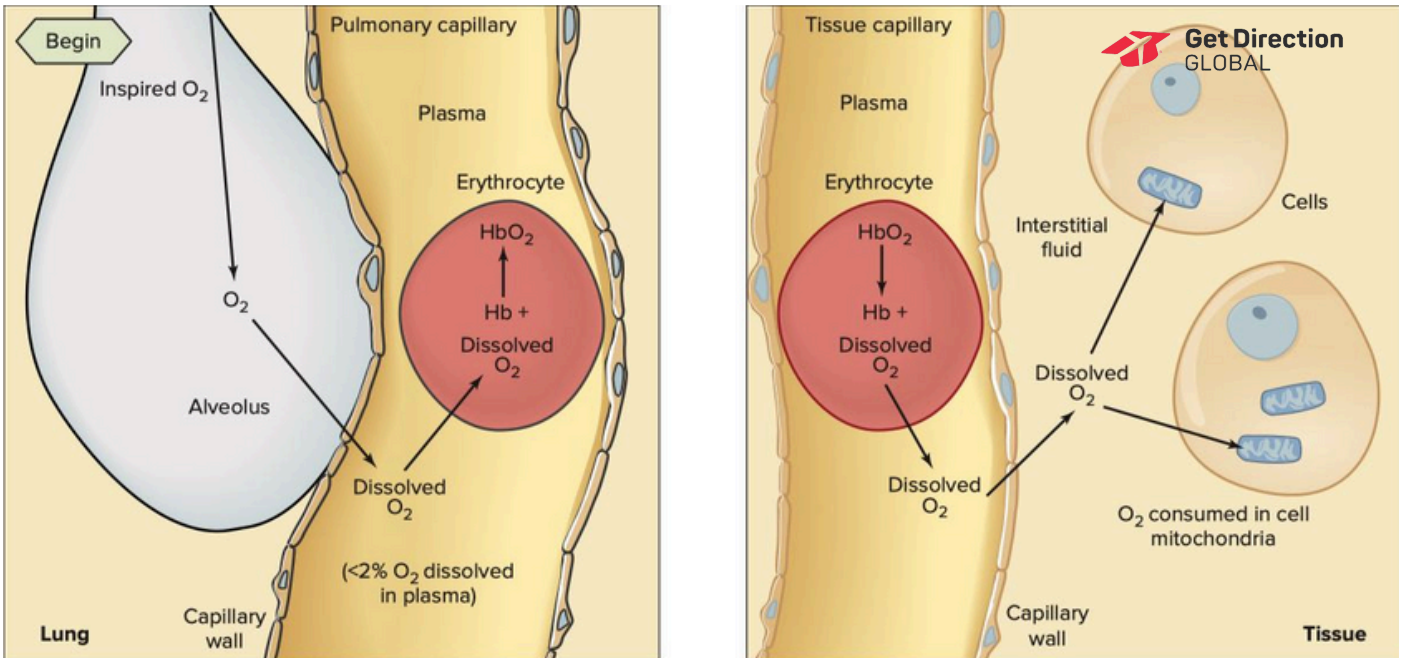
- **Oxygen Loading:**
  - In lungs
  - O2 diffuses into blood → into erythrocytes → binds to Iron Molecules in Haemoglobin
  - Haemoglobin → Becomes **OxyHaemoglobin**:
    - Assumes a new 3D shape
    - Becomes Ruby Red
- **Oxygen UnLoading:**
  - In Tissues
  - O2 detaches from Iron Molecules in Haemoglobin → Out of RBC, into blood → O2 into Tissue
  - OxyHaemoglobin → Becomes **DeOxyHaemoglobin:**
    - Resumes its former 2D shape
    - Becomes **Dark** Red
- **CO2 Transport:**
  - CO2 binds to Globin's Amino Acids; Rather than on the Haem Group



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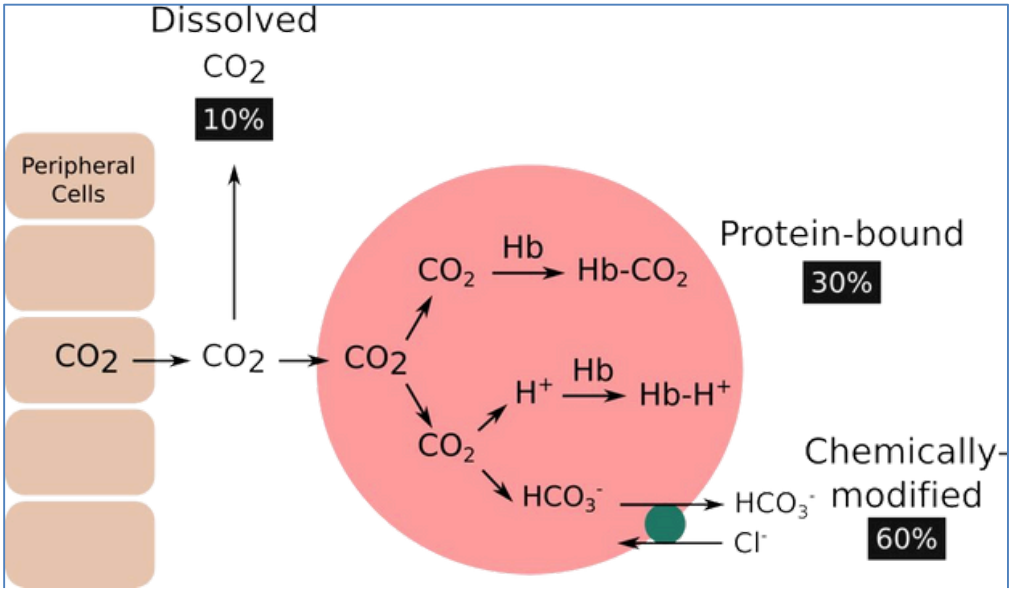

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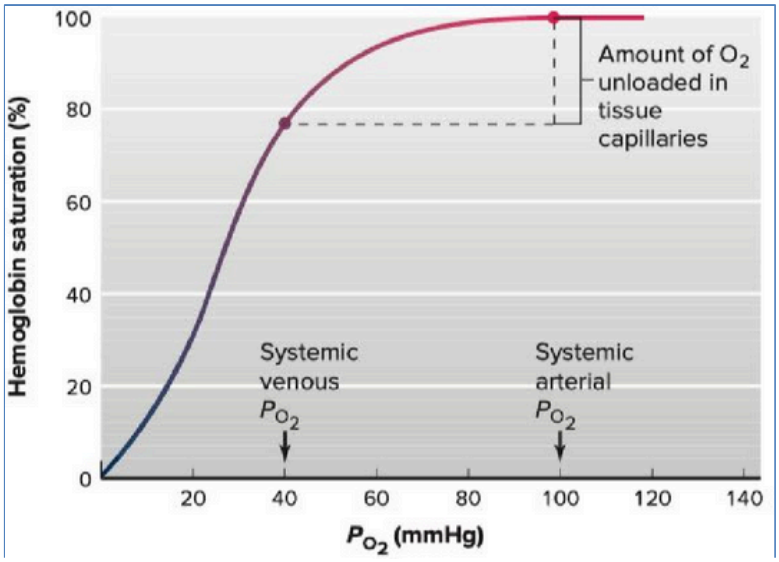
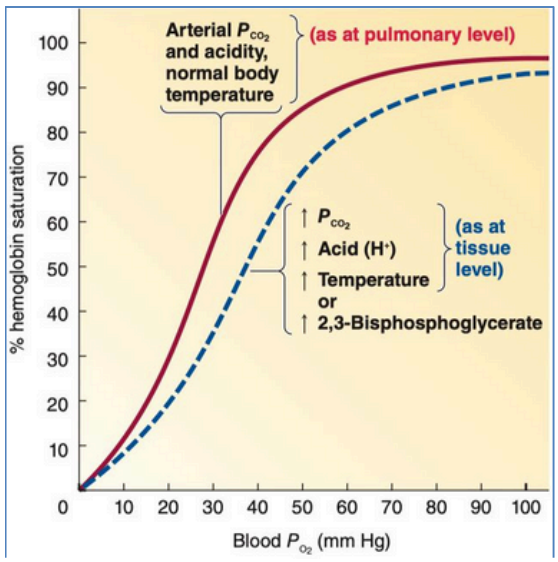
HAEMOGLOBIN – OXYGEN DISSOCIATION CURVE:

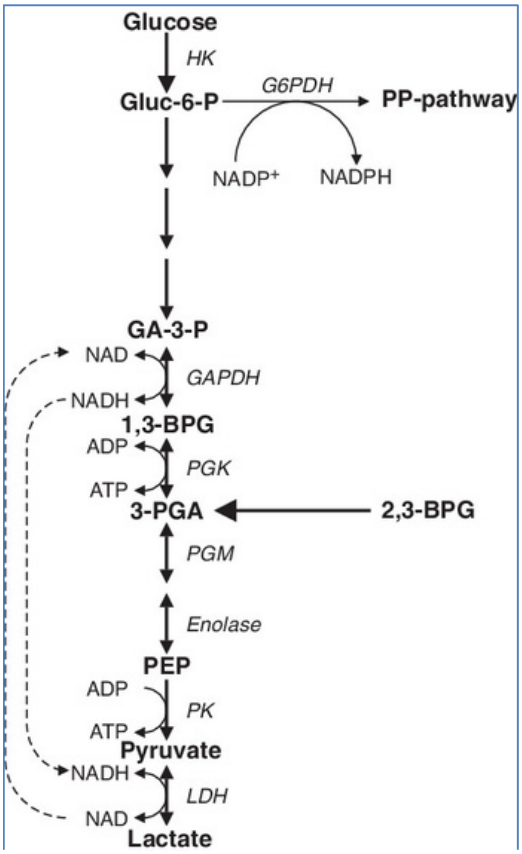
- Oxygen exchange operates between 95% Saturation (Arterial Blood) & 70% Saturation (Venous Blood)
- *P50* = Partial Pressure of O2 at which Haemoglobin is ½ saturated with O2 (Approx 26 mmHg)
- As the curve *shifts to the right*, O2 is given up *More Readily* to the Tissues
- During *CO2 Unloading* in the lungs, the curve *shifts to the left,* → O2 uptake increases



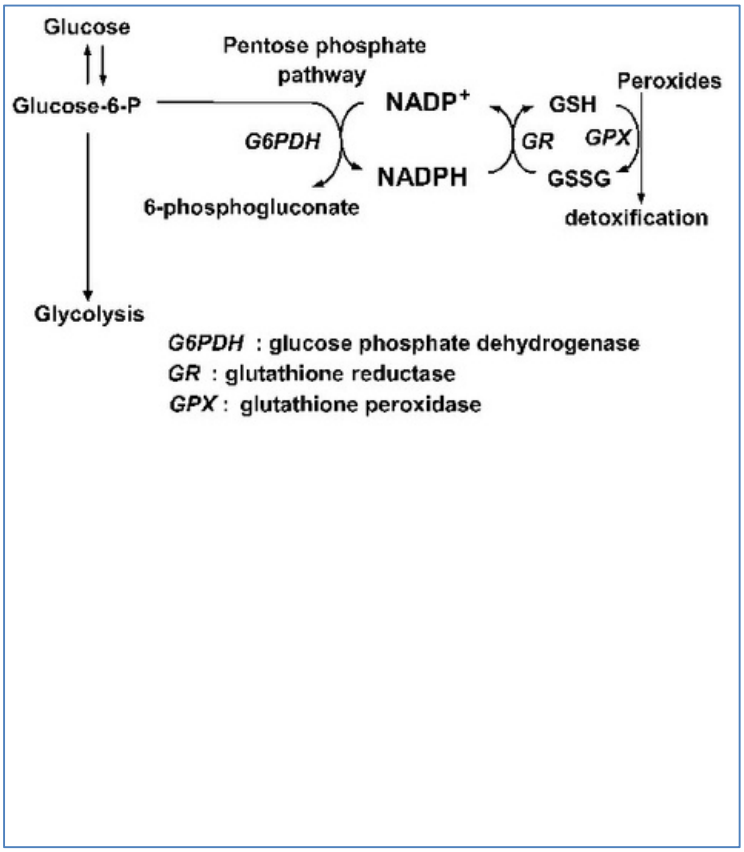


ERYTHROCYTE METABOLISM:

- ***RBC's don't have Mitochondria, so they're forced to generate energy via *anaerobic pathways*:**
  - o **Embden-Meyerhof Pathway:**
    - § Glucose metabolised to produce ATP
  - o **Pentose-Phosphate Pathway** (aka: Hexose Monophosphate Shunt)**:**
    - § Glucose metabolised to produce NADPH
    - § NADPH – used by *Methaemoglobin Reductase* to maintain Iron in *Ferrous Form* (Fe2+)
    - § Iron in the *Ferric Form* is useless because it doesn't bind oxygen → Leads to Oxidative Stress



Embden-Meyerhof Pathway

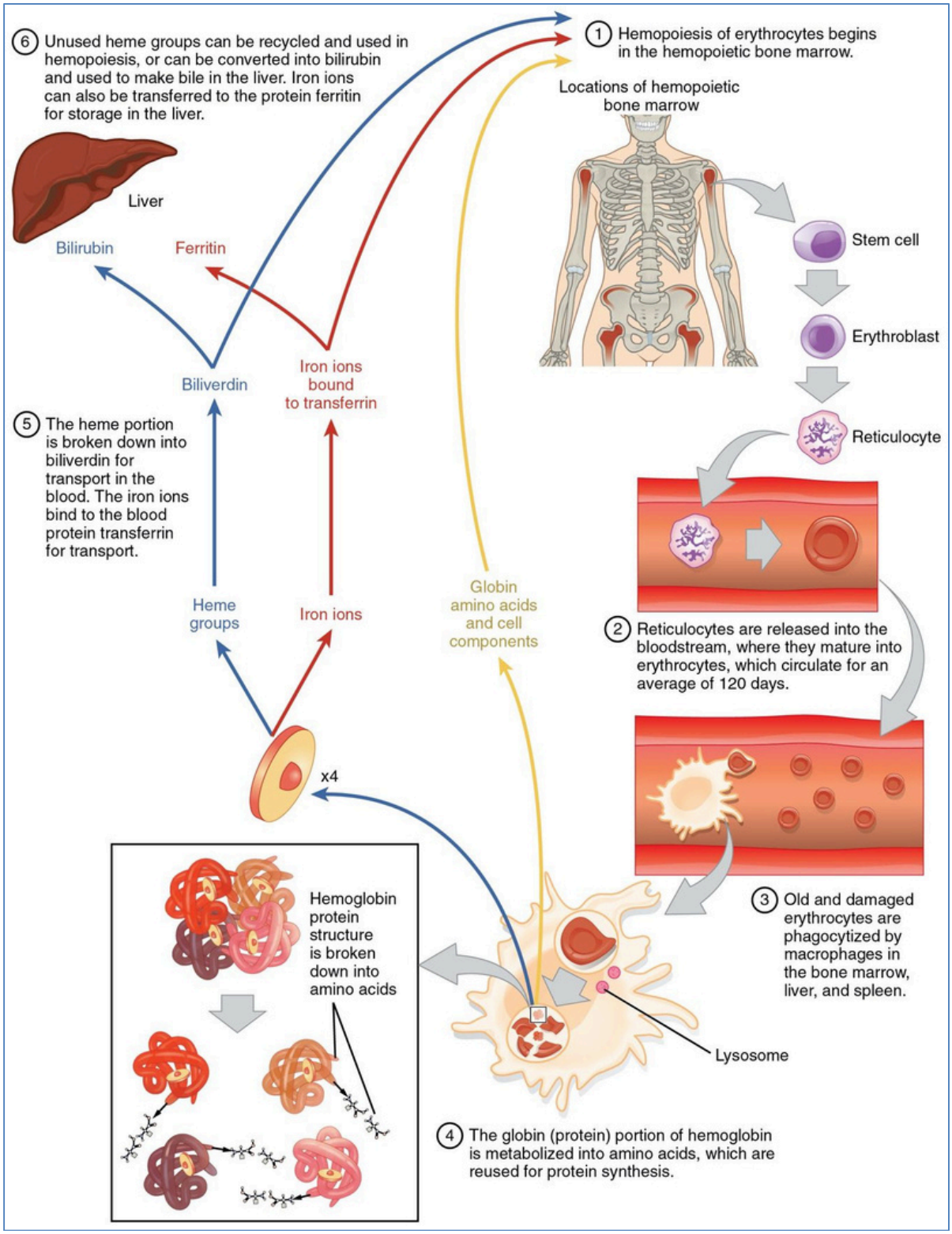


Shows the Pentose Phosphate Pathway
(Aka: Hexose Monophosphate Shunt)

ERYTHROCYTE DEATH:

- **Average Erythrocyte Lifespan:** 120 Days
- **Beyond 100 Days:**
  - o Glycolysis slows
  - o ATP levels decline
  - o Membrane becomes less flexible

- **Dying Cells – Removed by Macrophages in Spleen & Liver**
  - o **Iron is reused**:
    - § → Transported back to Bone Marrow (bound to *Transferrin*)
    - § → Stored as *Ferritin* in Bone Marrow
  - o **Protoporphyrin (Heme minus the Iron) is Metabolized**:
    - § Protoporphyrin → Bilirubin → Conjugated in Liver → Excreted in Bile → Faeces



HAEMOSTASIS/HEMOSTASIS:

HAEMOSTASIS/HEMOSTASIS:

Get Direction GLOBAL

What is Haemostasis?

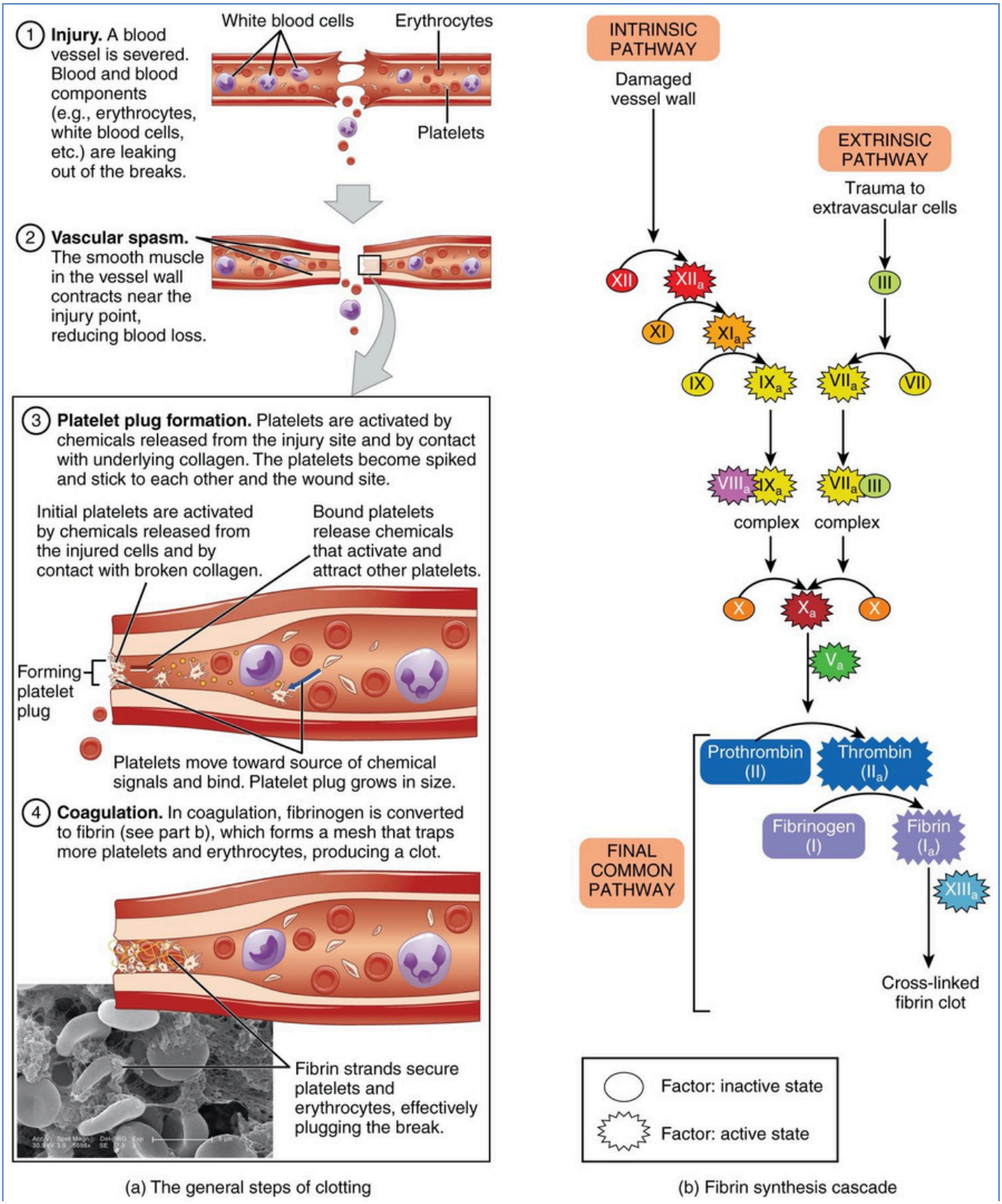
- **Literally means "Blood Halting"; Ie: Stopping Bleeding**
- **When a blood vessel is broken, Haemostasis is responsible for 'plugging' the hole**
- o Without Haemostasis, we would 'bleed-out' from even the smallest cuts

The Haemostatic Response is *Fast*, *Localised & Finely Regulated*

- o o Involves a chain reaction of 12 *Blood Coagulation FACTORS (Procoagulants)*
- o Also involves some other substances released by platelets and injured tissue cells

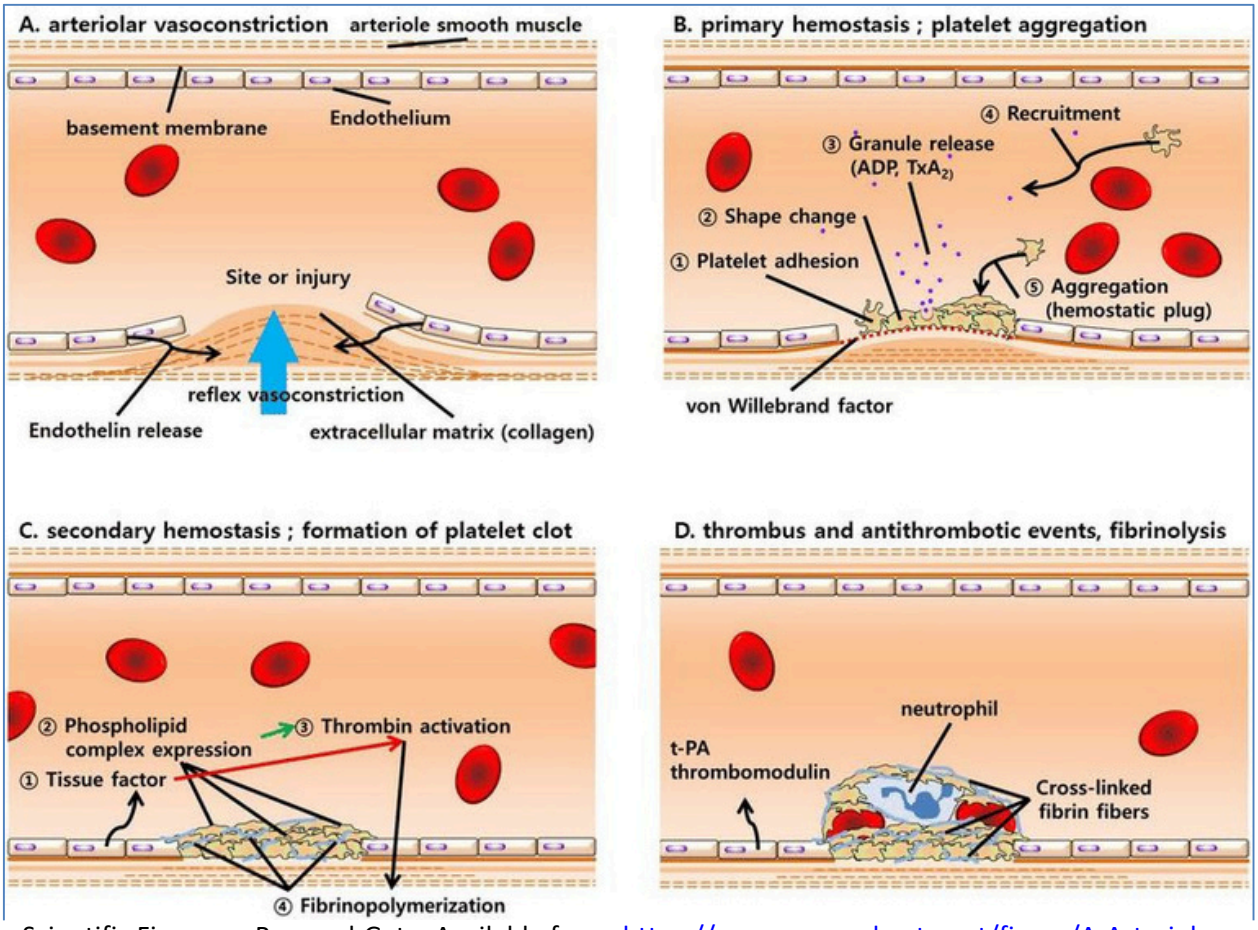
Plus Fibrin Stabilising Factor (FSF)

- **Results in a stable '*Platelet Plug*' (clot) at the site of injury**



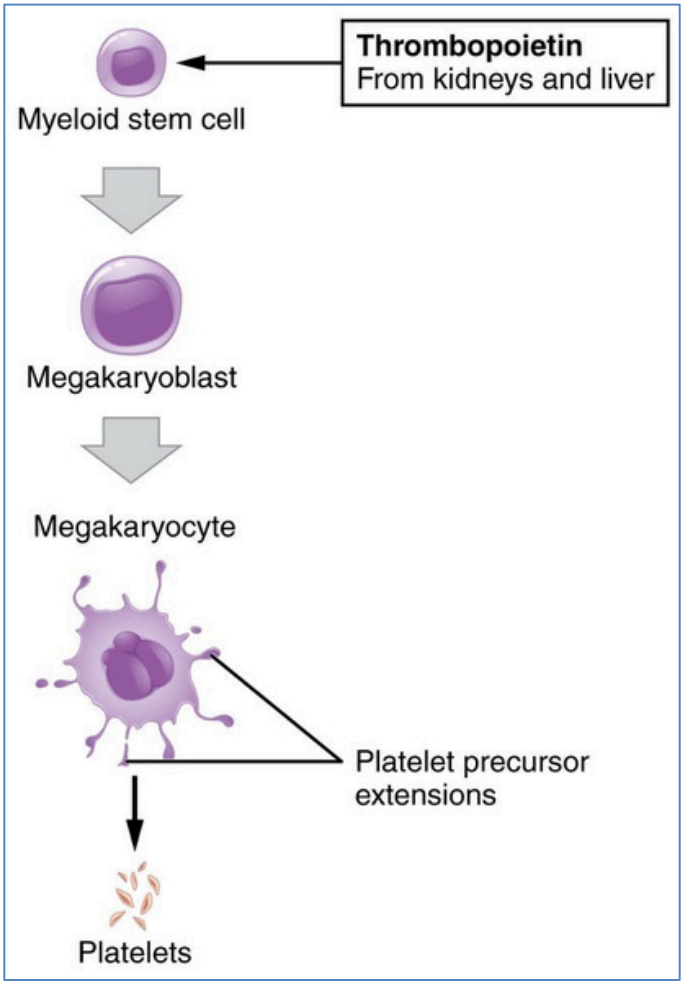
Important Components of Haemostasis:

- **Endothelial Cells:**
  - o = Simple Squamous Epithelium that Lines the blood vessels
  - o (Plus Small amount of Smooth Muscle around outside)
  - o **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
      Angiogenesis:
      - Formation of new vessels
      - Or Vessel Repair
  - o **Role in Haemostasis:**
    - § **Promote Plug Formation & Coagulation when injured**:
      - **Pro-Platelet Effects:**
        - o Exposure of SubEndothelial Collagen
        - o Produce Von Willebrand Factor (the glue)
      - **Pro-Coagulant Effects:**
      - o Exposure of Tissue Factor → Triggers Extrinsic P-way of Coagulation Cascade
        Anti-Fibrinolytic Effects: (pro-fibrin deposition)
        - o Blocks the Tissue Plasminogen Activator
    - § **Inhibits Plug Formation & Coagulation when intact**:
      - **Anti-Platelet Effects:**
      - o Nitric Oxide
        Anti-Coagulant Effects:
        - o Heparin
        - o & Thrombomodulin
      - **Fibrinolytic Effects:**
        - o Tissue Plasminogen Activator



Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/A-Arteriolar-vasoconstriction-occurs-immediately-by-the-reflex-mechanism-of-the-nervous_fig1_324188977

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



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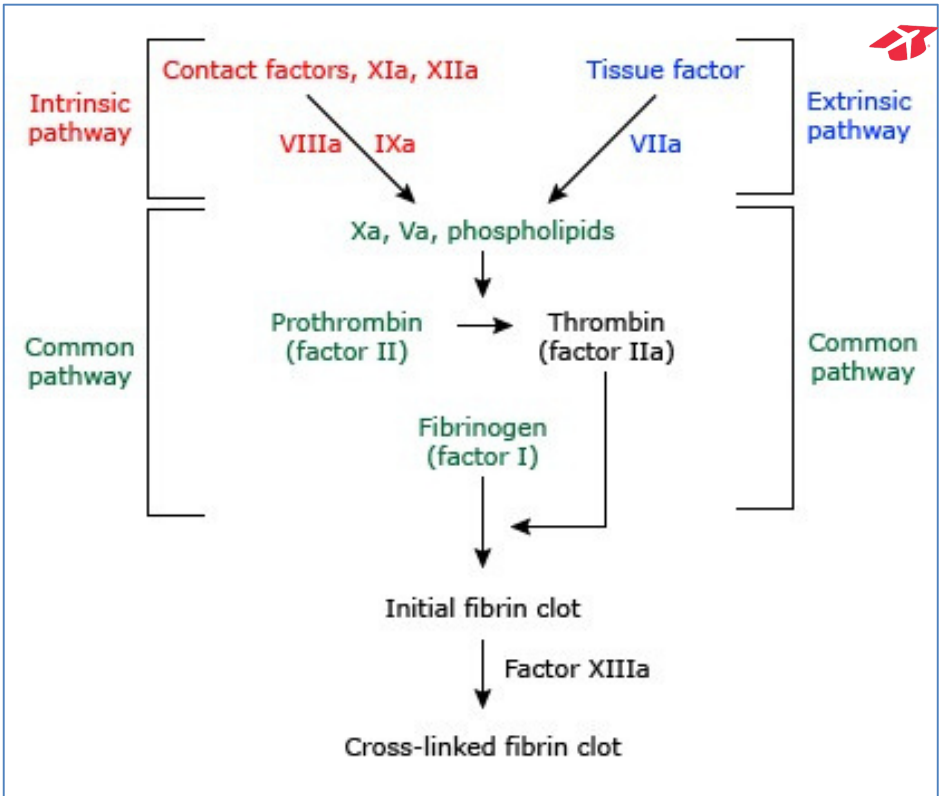
- **Coagulation Factors (Cascade):**
  - o **Role:** To stabilise primary platelet plug
    - § Protects plug from being washed away by flowing blood
  - o **Dependant on Coagulation Factors**
    - § Mainly produced in liver; (Some severe liver diseases → clotting deficiencies)
  - o **Has an Intrinsic, Extrinsic, & Common Pathway**
    - § (See simplified diagram below; explained in more detail later)

Clotting Factors

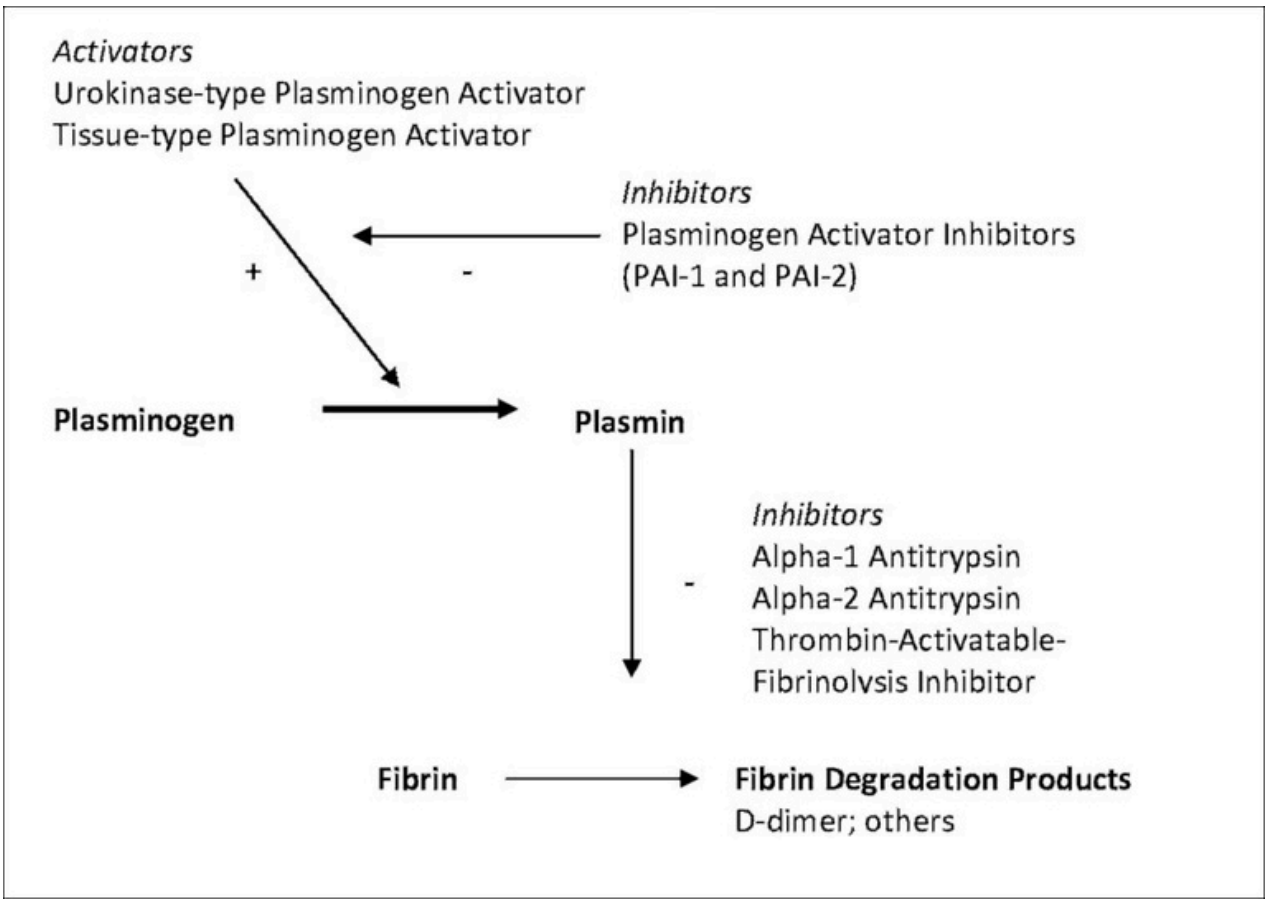
Factor number	Name	Type of molecule	Source	Pathway(s)
I	Fibrinogen	Plasma protein	Liver	Common; converted into fibrin
II	Prothrombin	Plasma protein	Liver*	Common; converted into thrombin
III	Tissue thromboplastin or tissue factor	Lipoprotein mixture	Damaged cells and platelets	Extrinsic
IV	Calcium ions	Inorganic ions in plasma	Diet, platelets, bone matrix	Entire process
V	Proaccelerin	Plasma protein	Liver, platelets	Extrinsic and intrinsic
VI	Not used	Not used	Not used	Not used
VII	Proconvertin	Plasma protein	Liver *	Extrinsic
VIII	Antihemolytic factor A	Plasma protein factor	Platelets and endothelial cells	Intrinsic; deficiency results in hemophilia A
IX	Antihemolytic factor B (plasma thromboplastin component)	Plasma protein	Liver*	Intrinsic; deficiency results in hemophilia B
X	Stuart–Prower factor (thrombokinase)	Protein	Liver*	Extrinsic and intrinsic
XI	Antihemolytic factor C (plasma thromboplastin antecedent)	Plasma protein	Liver	Intrinsic; deficiency results in hemophilia C
XII	Hageman factor	Plasma protein	Liver	Intrinsic; initiates clotting in vitro also activates plasmin
XIII	Fibrin-stabilizing factor	Plasma protein	Liver, platelets	Stabilizes fibrin; slows fibrinolysis

Table 18.1 *Vitamin K required.



(Simplified; Explained in detail later)

- **Plasm inogen/Plasm in (Responsible for Fibrinolysis):**
  - o Clots aren't permanent solutions to vessel injuries
  - o :. Fibrinolysis removes un-needed clots after healing has occurred...by:
    - § Blocking Coagulation Cascade:
    - § & By Breaking Down Fibrin:



3 PHASES OF HAEMOSTASIS:

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PHASE 1- PRIMARY HAEMOSTASIS:

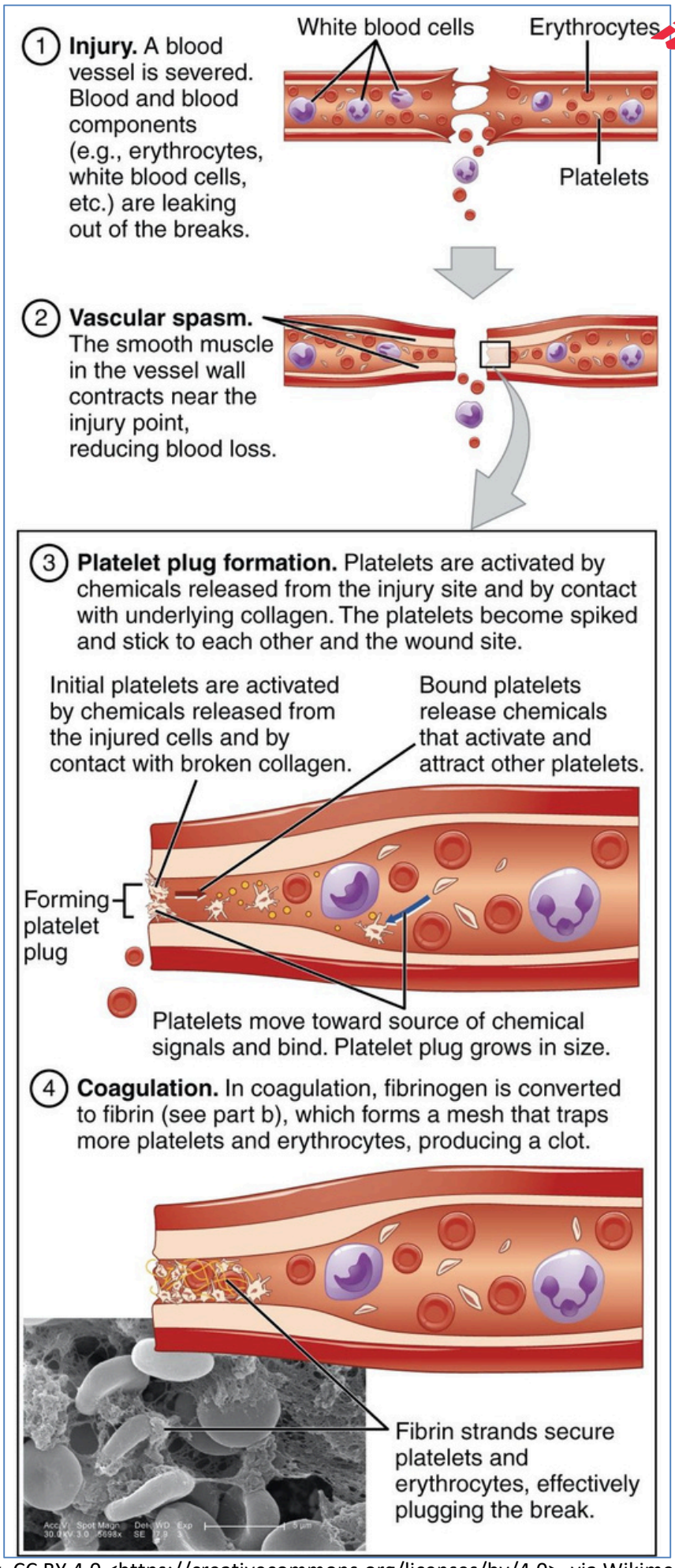
- **a) Vascular Spasms:**
  - o **Vasoconstriction**: The immediate response to vessel damage
  - o **Triggered by:**
    - § Local Neural Pain-Reflexes
    - § Chemicals released by: Endothelial Cells & Platelets
    - § Direct Smooth Muscle Injury
  - o **Significantly reduces blood loss**→ allows time for Platelet-Plug Formation & Clotting
  - o Most effective in smaller vessels

- **b) Primary Platelet Plug Formation:**
  - o **Platelets form a 'plug'** → *Temporarily* seals the break in vessel wall
  - o Platelets normally flow smoothly through an undamaged vessel .... HOWEVER....
  - o When vessel is damaged → ***Sub-Endothelial Collagen*** is exposed....
    - § Platelets ***(+ Von Willebrand Factor*** [glue]***)*** adhere strongly to the Collagen Fibres...
      - Platelets Activate → Conformational Change →
        - o Swell
        - o Form Spiked Processes
        - o Become 'Sticky'
      - → Primary Platelet-Plug 'Sandwich':

Surface Glycoproteins on Platelets
Von Willebrand Factor
Sub-Endothelial Collagen

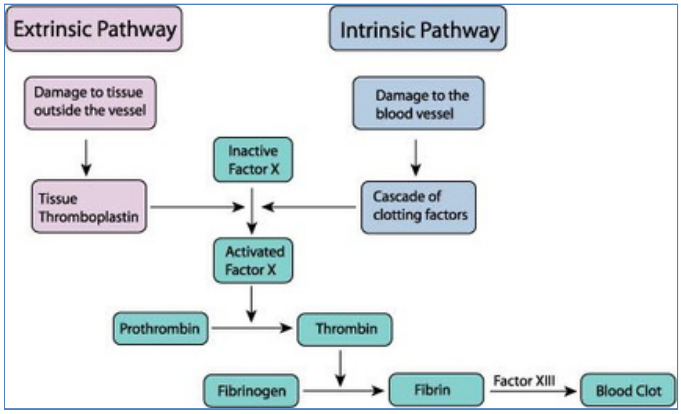
- **c) Platelet Aggregation:**
  - o Once attached, Platelets → Activated → ***Release Several Chemicals:***
    (Platelet Activation & Secretion Enhanced by Thrombin)
    - § **Serotonin:** Vasoconstrictor
    - § **ADP:** Potent Platelet-Aggregating Agent
    - § **Calcium (Factor IV):** A cofactor that *Activates* other *Inactive Pro-Coagulation Factors*
    - § **Thromboxane A2:** :. Important in Coagulation
      Vasoconstrictor
      Potent Platelet-Aggregating Agent
  - o Initiates a Positive Feedback Cycle → Activates & Attracts more & more Platelets
    - § Within 1min, a platelet plug is built → further reduces blood loss

- **d) Platelet-Plug Localisation:**
  - o **Prostacyclin:**
    - § A Prostaglandin Produced by *Intact* Endothelial Cells
    - § A Strong *Inhibitor* of Platelet Aggregation



PHASE 2- SECONDARY HAEMOSTASIS:

- **a) Coagulation Cascade:**
  - o **Coagulation** (Ie: Blood 'Clotting'): Where Blood; Liquid → Gel
    - § = Series of enzymatic conversions of *Inactive→ Active Coagulation Factors*
  - o **Intrinsic Pathway:**
    - § **→Triggered by Exposed Sub-Endothelial Collagen**
    - § All factors needed for clotting are in the blood
  - o **Extrinsic Pathway:**
    - § →**Triggered by Exposed Tissue Factor** (Factor III)



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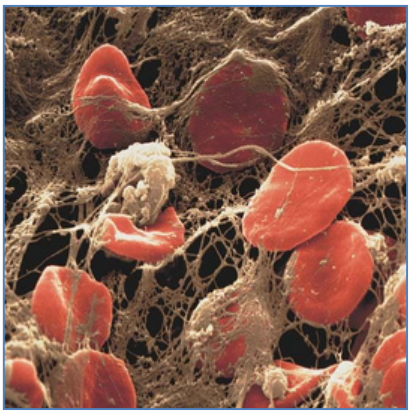
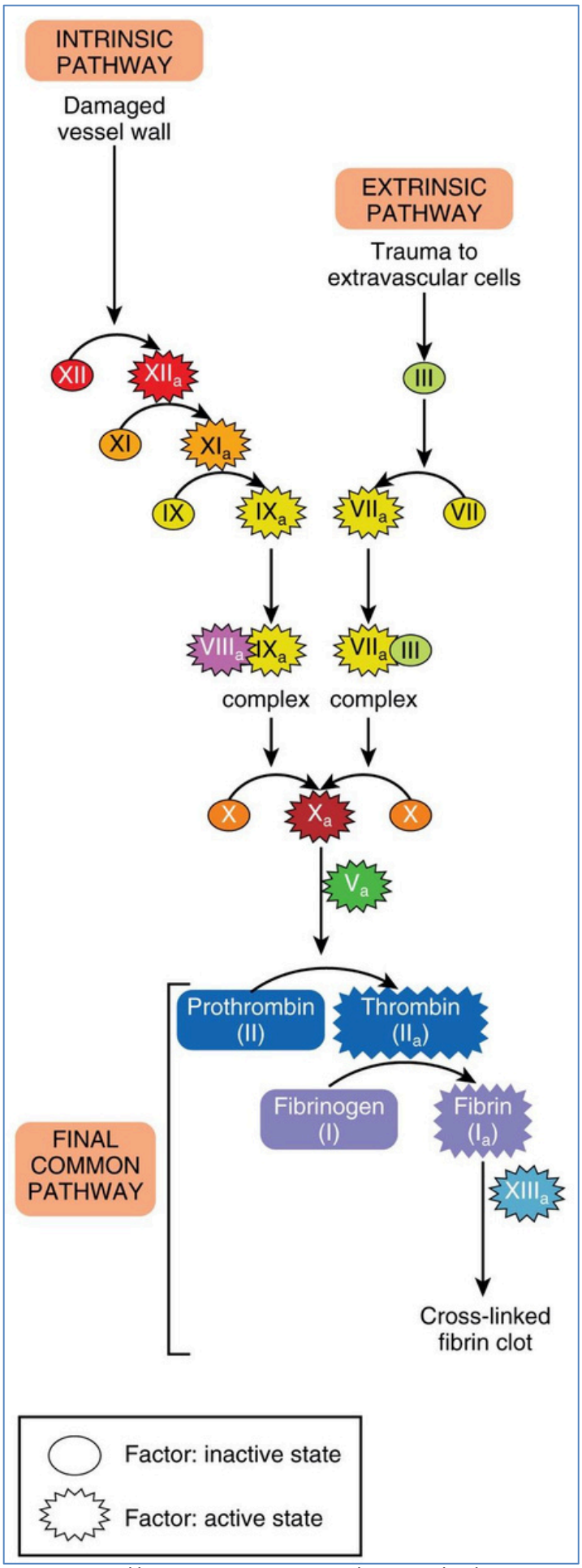


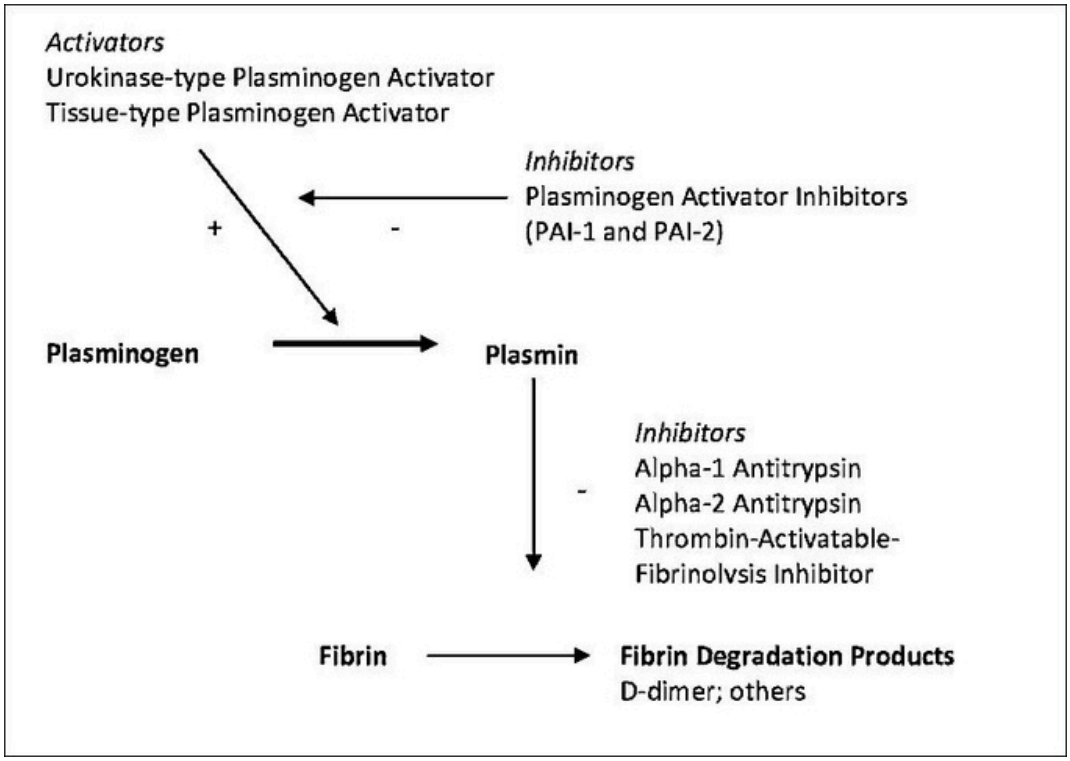
  - o **Common Pathway:**
    - § Both Pathways eventually lead to ***Activation of Factor-X***
      - **1- Activated Factor-X** combines with other factors→
      - **2- Prothrombin Activator** is formed...
      - **3- Prothrombin Activator**; converts the plasma-protein: ***Prothrombin → Thrombin***
- **b) Fibrin Deposition:**
  - o **4- Thrombin** Catalyses Conversion & Deposition of ***Fibrinogen→Fibrin***
    - § Also **+Ve Feedback** on Coagulation Cascade (Amplification of Prothrombin Activation)
  - o **5- Fibrin** Mesh →+ ***Active Factor-XIII*** → Stabilises the Platelet-Plug → Seals the hole
    - § **Primary Platelet Plug** + *Mesh* **→ Secondary Platelet Plug**
- **c) Regulation:**
  - o **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
  - o **AntiCoagulants:**
    - § Factors inhibiting clot-formation
    - § These factors Dominate in Undamaged-Vessels
- **d) Coagulation Localisation:**
  - o **Activation of Coagulation Factors is Restricted to Sites of Exposed Phospholipids:**
    - § Ie: Phospholipids on platelet membranes
    - § Platelet Phospholipids are exposed by Platelet-Activation
  - o **Anticoagulants:** See Above
    - § **Tissue Factor Pathway Inhibitor:**
      - (Inhibits Extrinsic Pathway)
      - → Inactivates Factor-Xa
      - → Inhibits [Factor-VIIa – Tissue Factor Complex]
    - § **Thrombomodulin:**
      - → Blocks Coagulation Cascade
      - → Binds Thrombin – Fibrinogen can't convert to Fibrin
        - o → Then Activates Protein-C
    - § **Protein C & Protein S:**
      - →Combine to *Inactivate Factor-Va & Factor-VIIIa*

      Antithrombin *(+ Heparin)*:
      - →Inhibits Thrombin
      - →Inhibits Factor-Xa & Factor-XIa

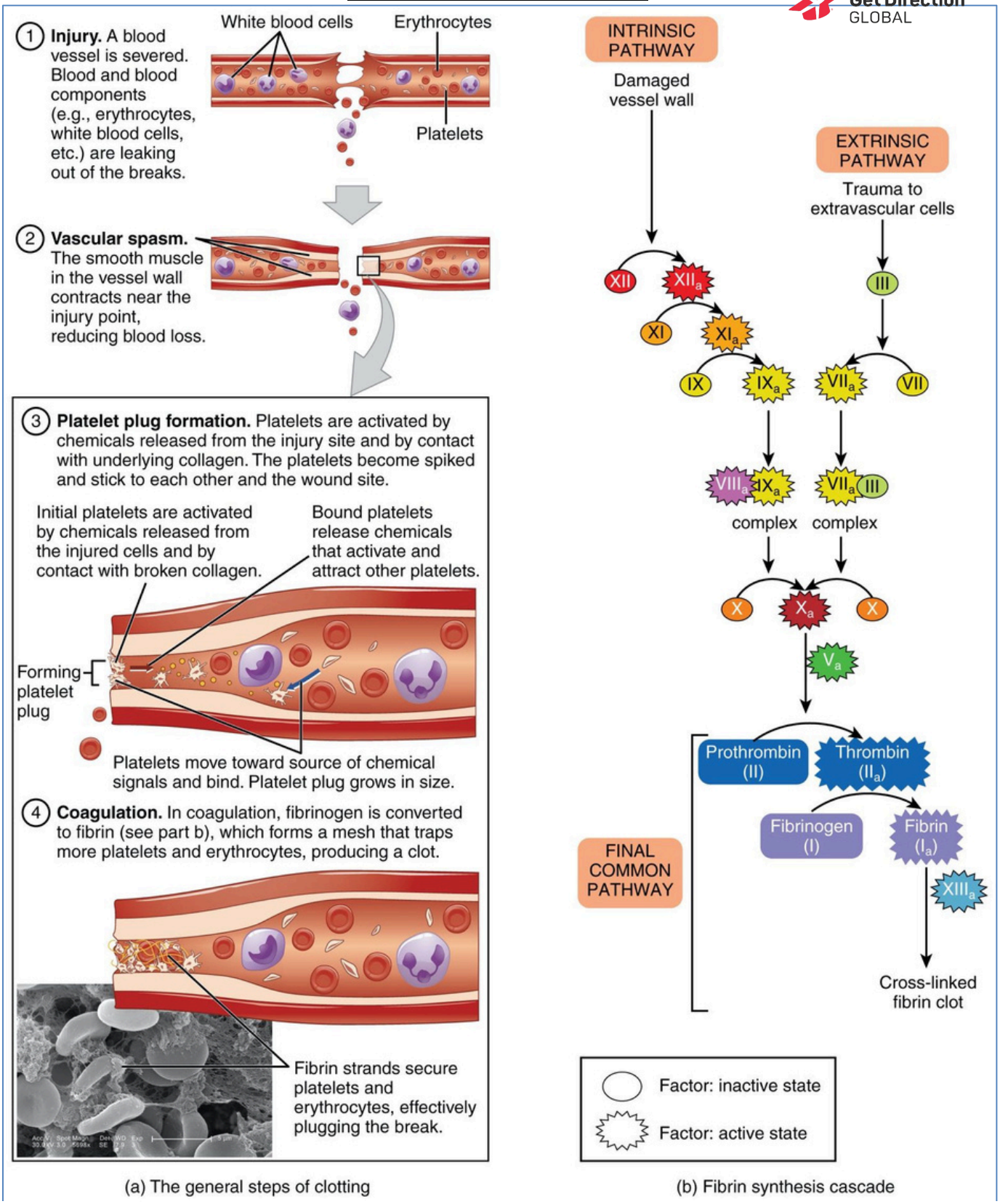


PHASE 3- FIBRINOLYSIS:

- Clots aren't permanent solutions to vessel injuries
- :. Fibrinolysis removes un-needed clots after healing has occurred...by:
- **Blocking Coagulation Cascade:**
  - o **Thrombomodulin:**
    - § Blocks Thrombin from activating Fibrinogen :. No Fibrin Deposition
- **& By Breaking Down Fibrin:**
  - o **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*
  - o **Results in Fibrin Degradation Products (FDP's):**
    - § Eg: D-Dimer
    - § Can be measured in the blood
    - § Tested to see whether there has been excessive blood clotting



REVIEW OF THE W HOLE PROCESS:



THE ROLE OF BLOOD IN THE IMMUNE SYSTEM

THE ROLE OF BLOOD IN THE IMMUNE SYSTEM

(Basic Summary; More Detail in our Immunology/Rheumatology Subject)

The Immune System:

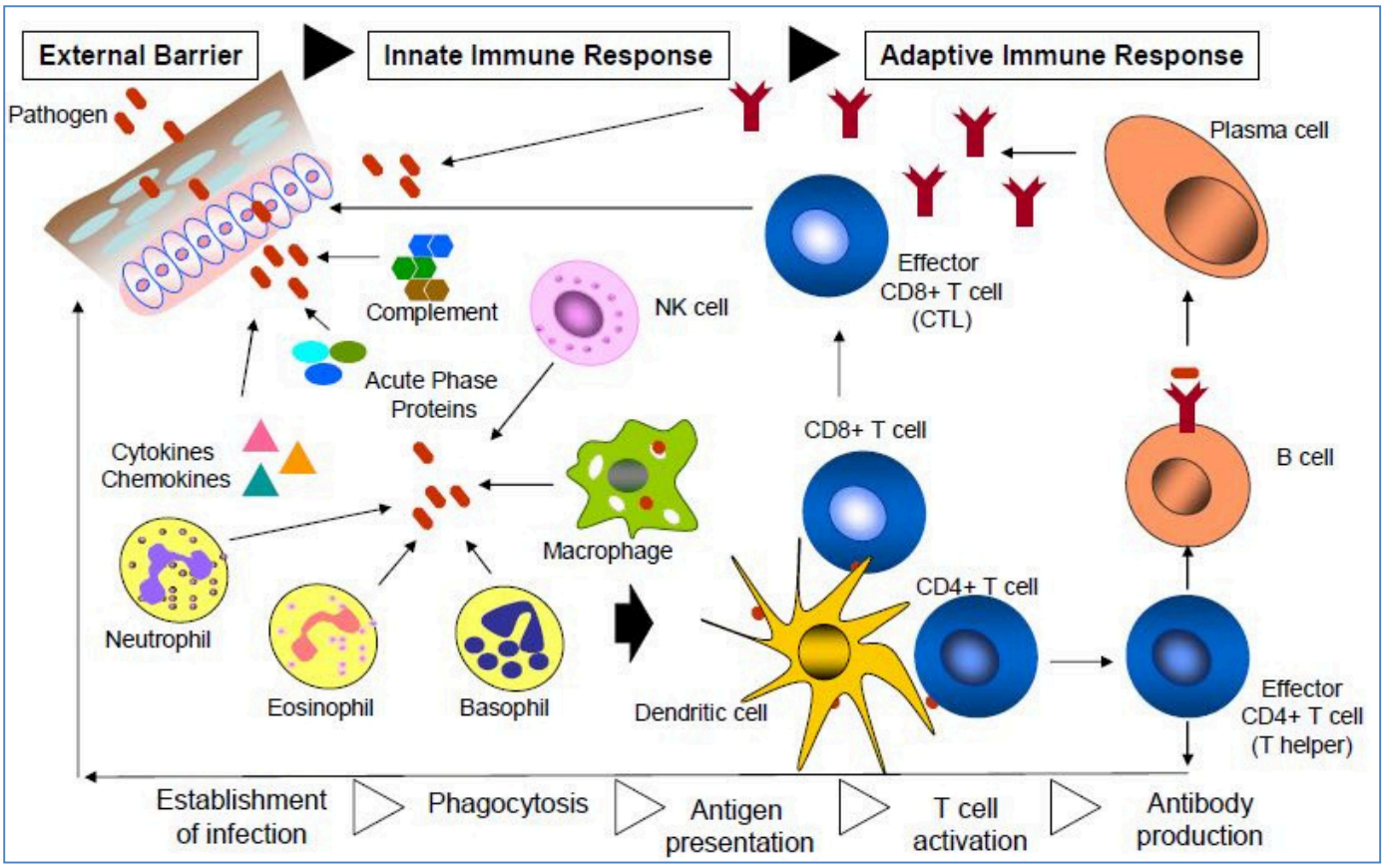
- The immune system is more a ***functional*** **system rather than an** ***anatomical*** **or** ***organ-based*** system
- **Consists of:**
  - o a diverse array of molecules
  - o -and trillions of immune cells (especially lymphocytes)
  - o These molecules & immune cells inhabit lymphoid tissues & circulate in body fluids
- **Functions to protect the body from:**
  - o Most infectious microorganisms
  - o Cancer cells
  - o Transplanted organs
  - o Grafts
  - o 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
  - o Note: Infection Doesn't necessarily lead to disease; Depends on:
    - § Route of entry
    - § Number of pathogens
    - § Immune status of host

Basic Diagram of the Immune System:

- Note that there is an **External Barrier**, An **Innate Immune Response** & an **Adaptive Immune Response**



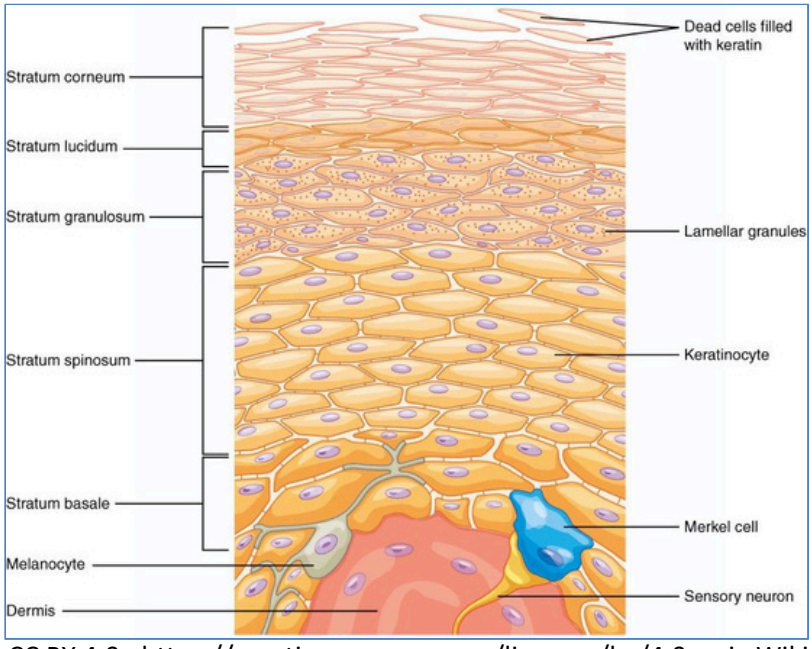
INNATE VS ADAPTIVE IMMUNE SYSTEM

INNATE (NON-SPECIFIC) IMMUNE SYSTEM:

- **Features:**
  - o Already in place at birth
  - o Is always prepared
  - o Responds within minutes

- **Role:**
  - o Protects the body from all foreign substances
  - o Are often sufficient to ward off invading pathogens single-handedly
  - o Essentially, it exists to **reduce the workload of the adaptive system**

- **1st Line of Defence: Surface Barriers:**
  - o **Role: Prevents Entry of Pathogen**
    - § **Skin**
      - Stratified
      - Heavily keratinised



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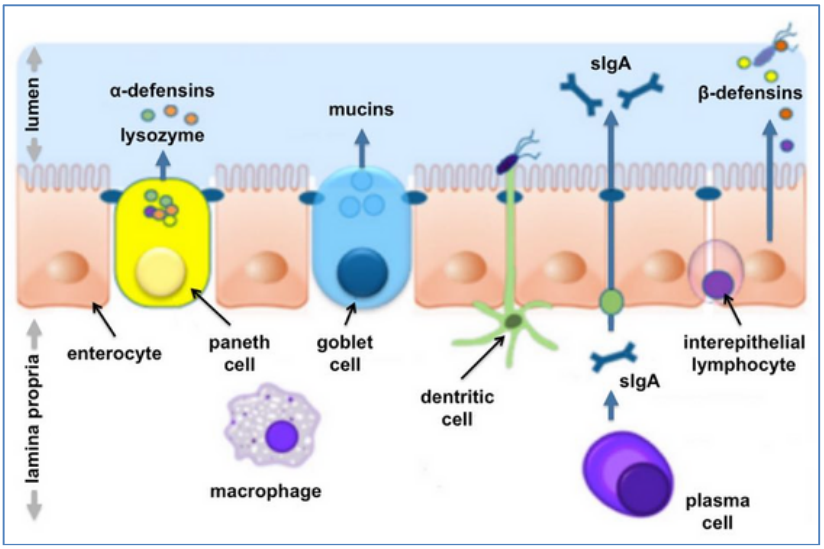
    - § **Mucous membranes**
      - Lysozyme: enzyme found in saliva & tears →destroy bacteria
      - Sticky Mucus: in digestive & respiratory tracts →traps bacteria
      - Cilia – nasal & respiratory →sweep bacteria into mouth→swallowed
      - Acid secretion: skin, vagina, stomach →kills microbes



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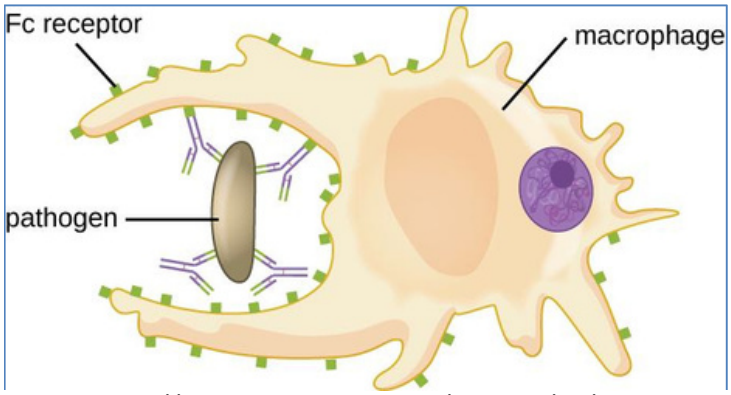
- **2nd Line of Defence: Internal Defences:**
  - **Role: Prevents Spread of Pathogen If Surface Barriers are Breached**
    - **Macrophages** – Large phagocytic cells



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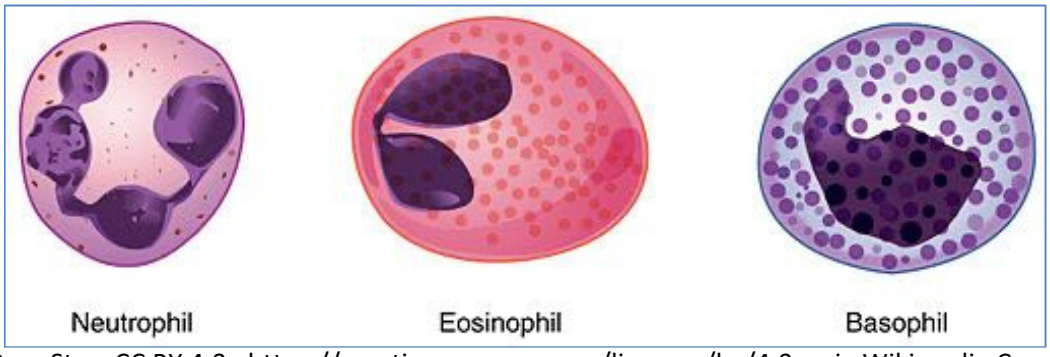
    - **Granulocytes –** possess cytoplasmic granules
      - **Neutrophils** –they release toxic chemicals into the extracellular fluid, killing both the target and themselves (kamikaze)
      - **Eosinophils** – another type of white blood cell – **kill parasitic worms**
      - **Basophils** – important in allergic reactions



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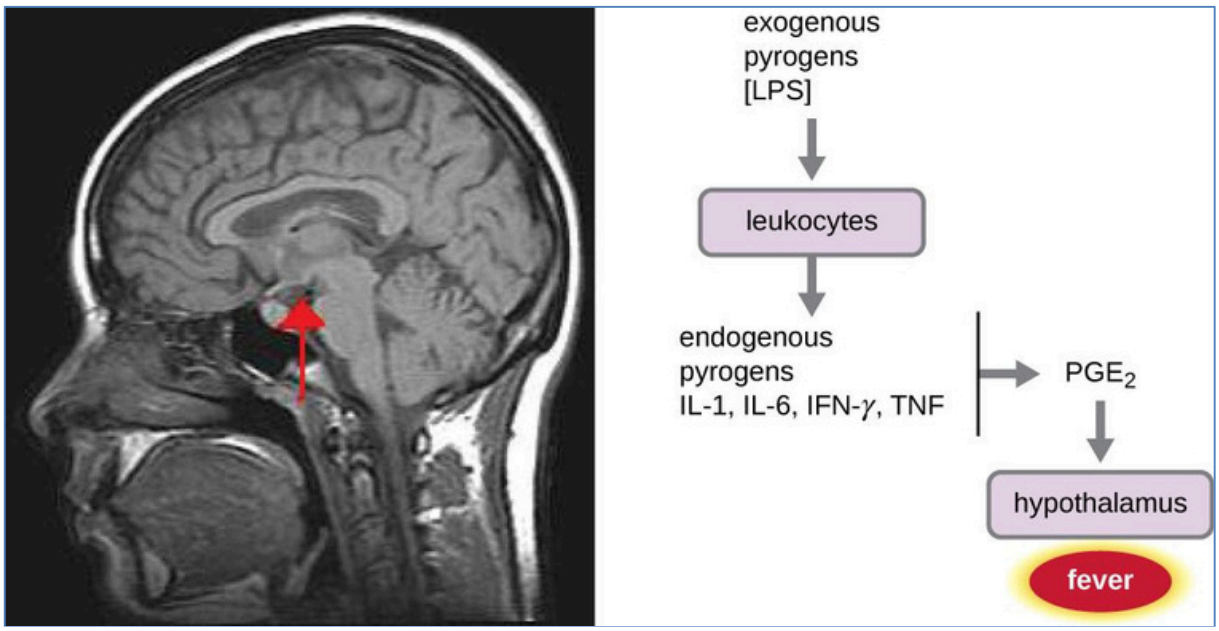
    - **Fever**
      - When exposed to foreigners, leukocytes & macrophages secrete pyrogens → increases the body's thermostat
      - Increases metabolic rate, kills microbes, speeds up repair



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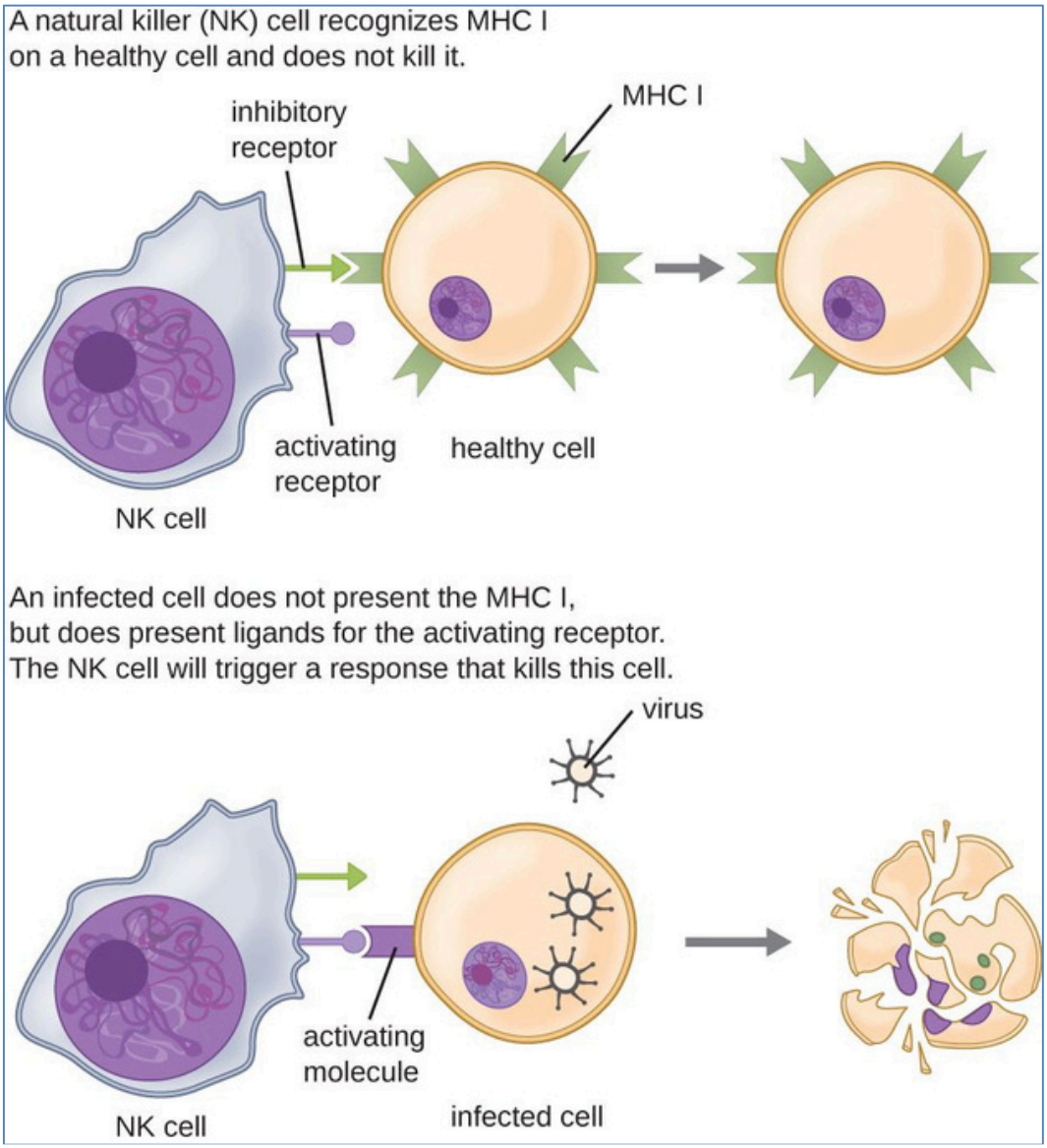
§ **Natural Killer cells**
- Police the body in blood & lymph
- Can lyse & kill cancer cells & virus-infected cells
- Target all cells that lack 'self' surface receptors (non-specific)
- Kill by latching onto invaders and inducing apoptosis
- Also secrete potent chemicals that promote inflammation



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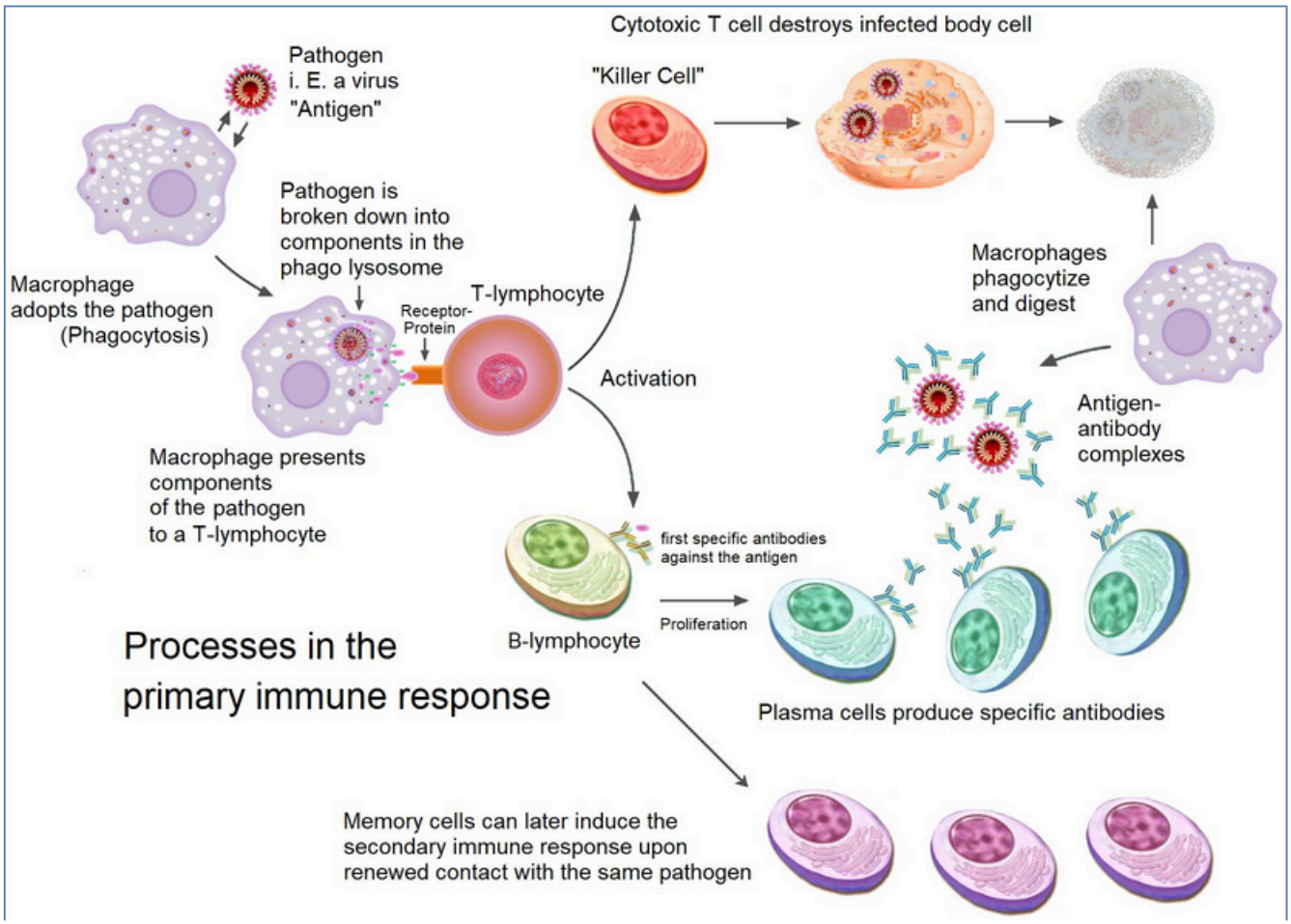
§ **Antimicrobial proteins**
- Either attack microbes directly or reduce their reproductive ability
- –'Interferons' & 'compliment'

§ **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:

- *Think of the Adaptive Immune System as "The body's elite special forces" – with high-tech weapons*
- **Features:**
  - o **>It is Specific:** recognises *particular* pathogens/antigens
  - o **>It is Systemic:** immunity isn't restricted to initial infection site
  - o **>It has Memory** Adaptive responses are called into action as 'reinforcements'
- **Roles:**
  - o Tremendously amplifies the inflammatory response
  - o Attack specific foreign substances – Incl: Antigens and abnormal body cells
  - o mounts stronger attacks on previously encountered pathogens
- **The body's 3rd line of defence (Humoral & Cellular Immunity):**
  - o **a) CELLULAR IMMUNITY:**
    - § 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



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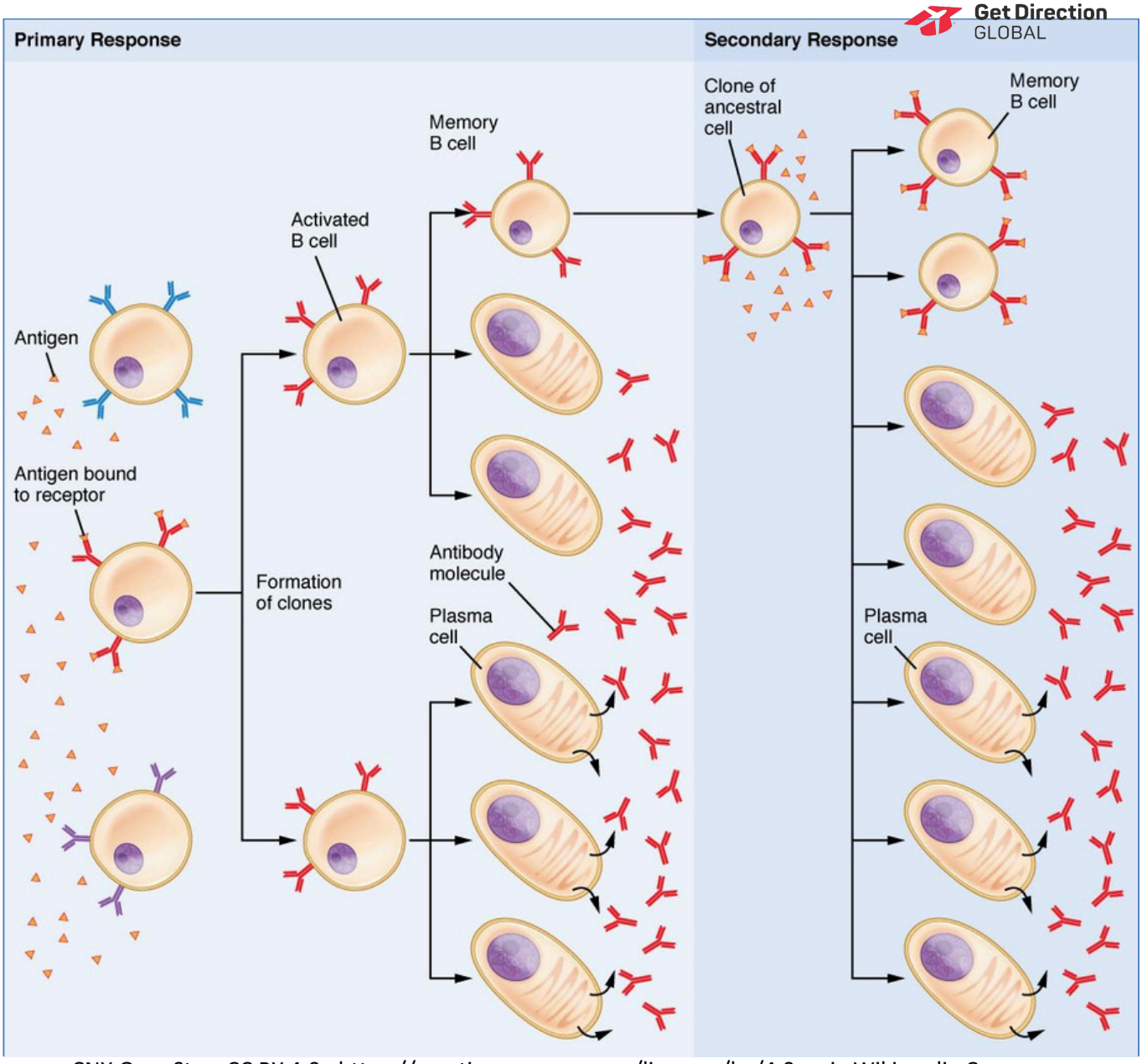
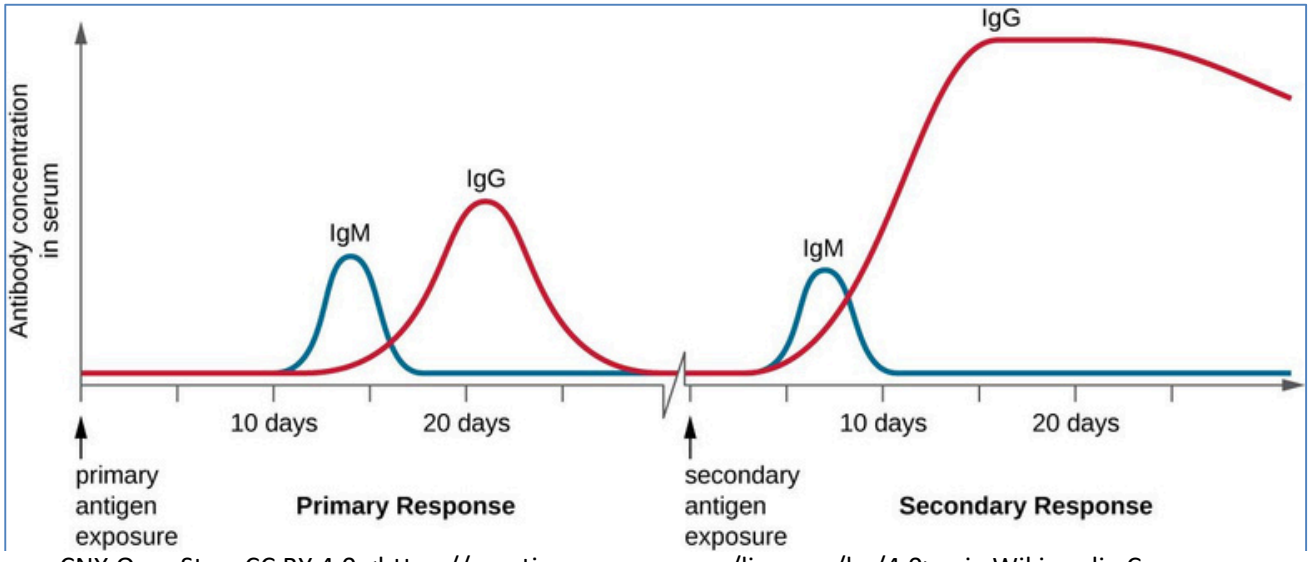
- o **b) HUMORAL IMMUNITY** (aka: Antibody-mediated immunity) -Immunity can be **transferred** from person-person **via serum**
  - § **B Cells (B-Lymphocytes**)
  - §
    - **Make antibodies** against soluble antigens

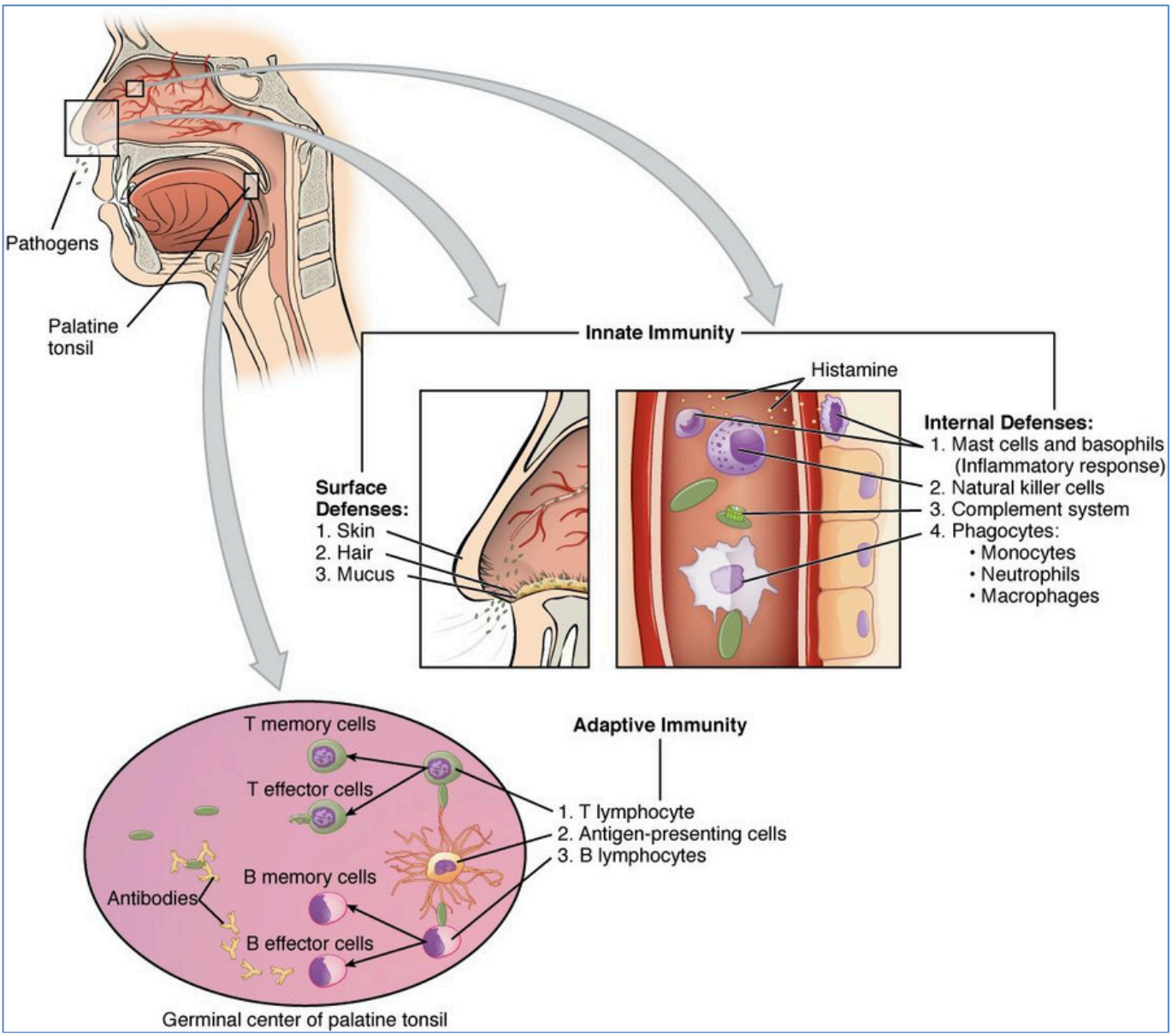
    Antibodies (Immunoglobulins):
    - Circulate freely in blood & lymph
    - **Neutralises** bacteria/toxins/& viruses →marks for destruction by phagocytes or com plim ent



(Note: Once the body has Memory B-Cells from the first immune response, the immune reaction to the second exposure is m uch quicker and has a higher antibody yield. Is the prim ary m echanism behind vaccines)



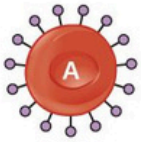
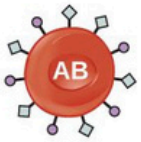
The W hole Im m une System Sum m ary:



BLOOD GROUPS, TRANSFUSION & BLOOD PRODUCTS.

BLOOD GROUP ANTIGENS:

- There are ≈400 known RBC Antigens
- We are only concerned with 2 categories; the **ABO & Rh Antigens**
- **1- 'ABO' Blood Group Antigens:**
  - o **Sugar Chains emanating from the RBC membrane**
  - o **Determines the 'A/B/AB/O' blood types**
    - § A-Antigen B-
    - § Antigen A & B-
    - § Antigens H-
    - § Antigen (O-Type)

	Blood Type			
	A	**B**	**AB**	**O**
Red blood cell type				
Isohemag-glutinins	 Anti-B	 Anti-A	None	 Anti-A and Anti-B
Antigens on red blood cell	 A antigen	 B antigen	 A and B antigens	None

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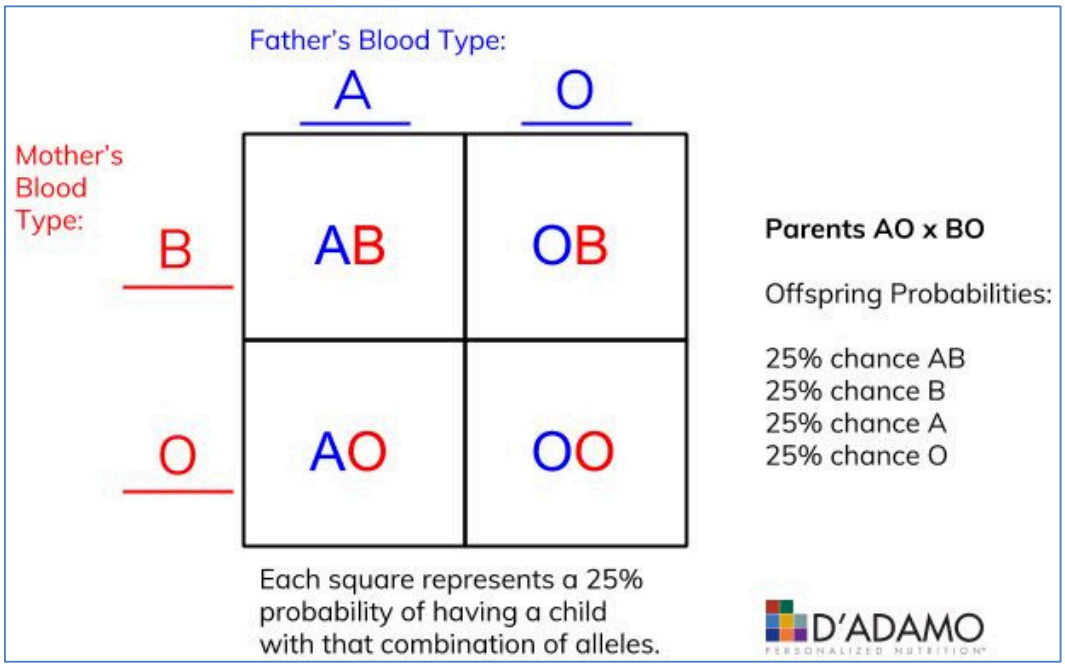
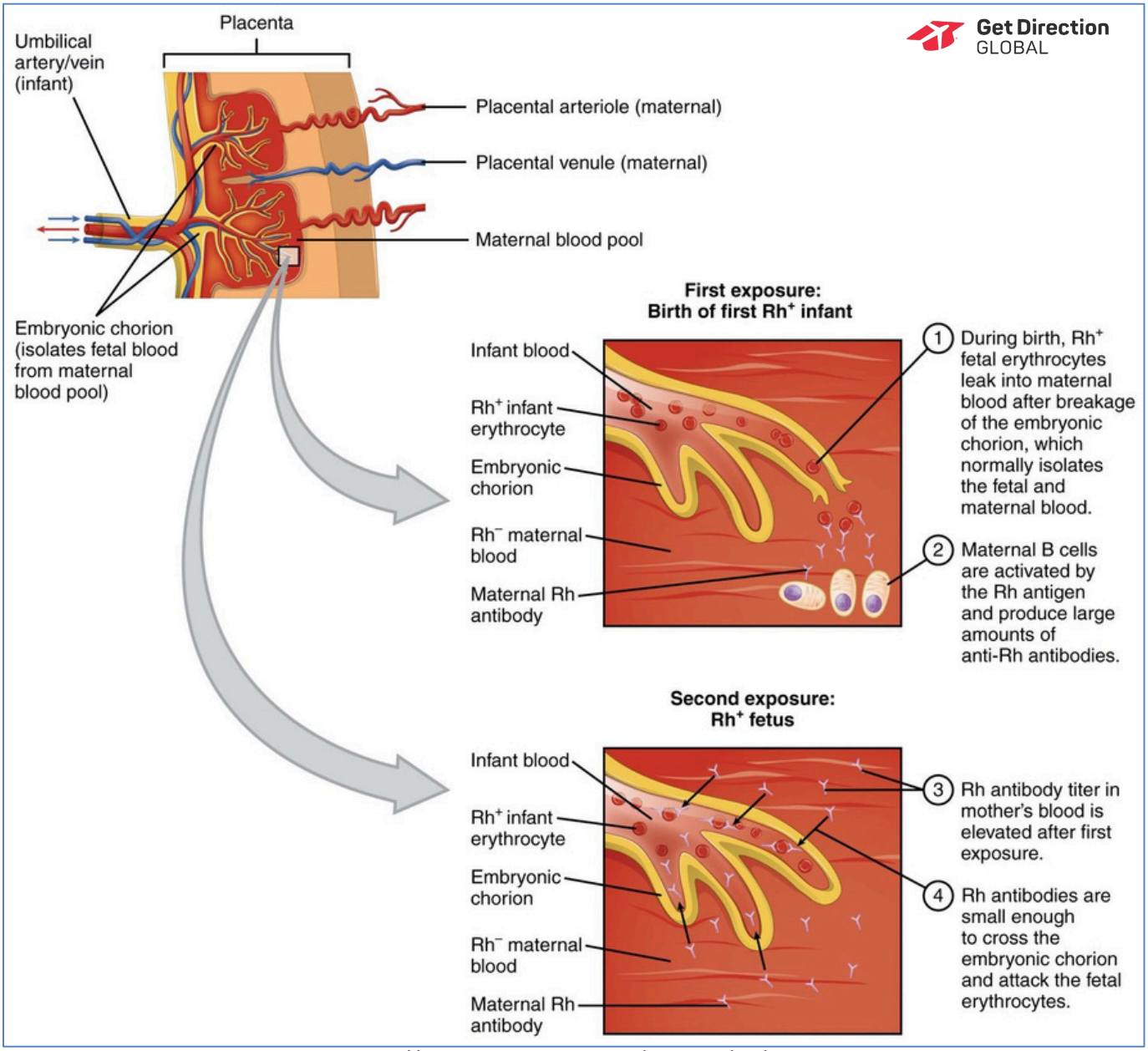
- o **Exist due to 3 allelic genes (A, B & O)**
  - § A & B alleles can show *Codominance* (AB-Type)
  - § A & B alleles are Dominant over the 'O' allele
  - § Homozygous 'OO' is dominant over A or B alleles



Source: D'adamo.

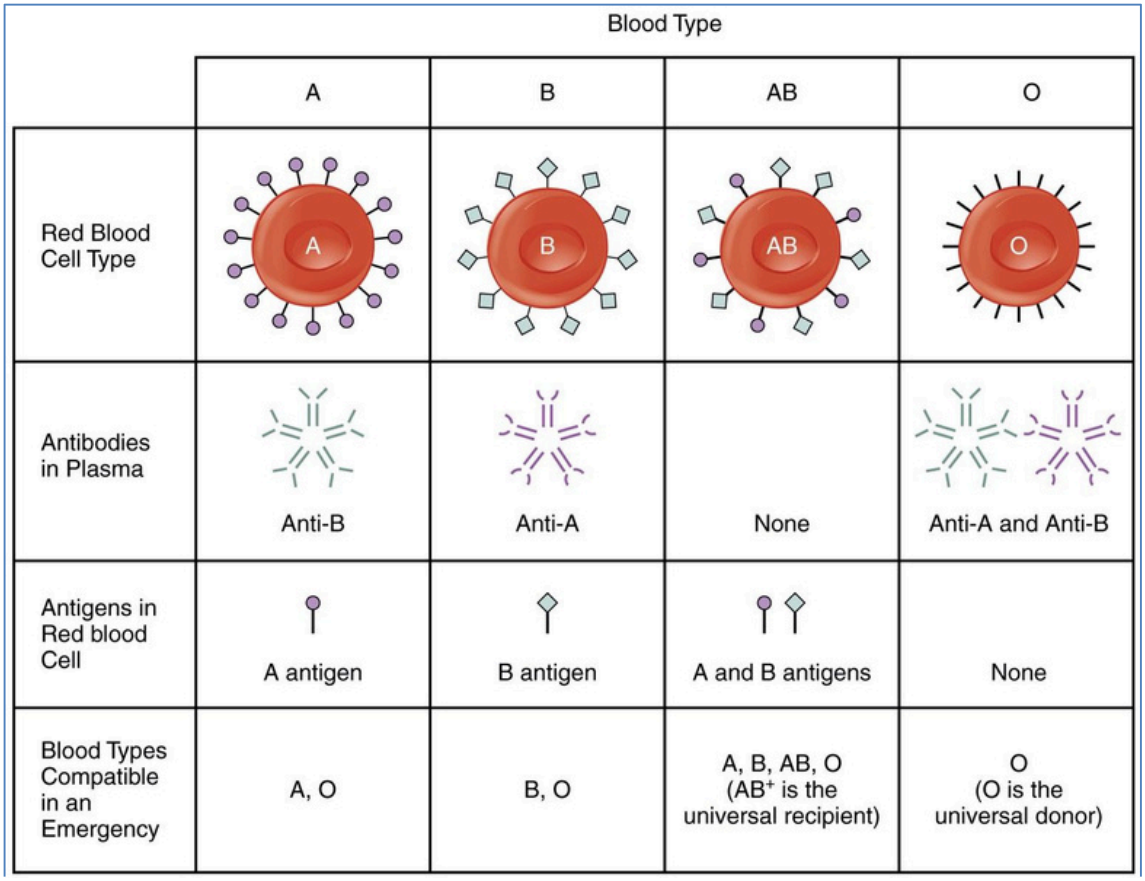
- **2- 'Rh' (Rhesus/Rh-D) Blood Group Antigens:**
  - o Membrane-Bound protein on RBC
  - o **Presence/Absence of the Rh'D'-Gene determines +ve/-ve blood type**
    - § Presence of RhD → Positive
    - § Absence of RhD → Negative
  - o **Relevance in Transfusions:**
    - § **Rh-Positive Patients:** Can receive *either* Rh-Positive OR Rh-Negative Blood
    - § **Rh-Negative Patients:** Should ONLY receive Rh-Negative Blood (except in extreme emergencies and Rh-Negative blood is unavailable)
  - o **Relevance in Pregnancy:**
    - § **If the mother is Rh-Negative, but the fetus is (potentially) Rh-Positive →**
      - → 'Rh-Incompatibility'
      - (If father is Rh-Positive or father's Rh-status is unknown)
    - § Normally, maternal and fetal blood don't mix, but sometimes a **sensitizing event** can occur, causing fetal blood to contact maternal blood
      - Eg: Abdominal trauma during pregnancy
      - Eg: Amniocentesis
      - Eg: Miscarriage
      - Eg: Ectopic pregnancy
      - Eg: Chorionic villus sampling
      - Eg: Bleeding during pregnancy
    - § **If Rh-Negative mother gets sensitized to Rh-Positive Fetus →**
      - → Mother's immune system produces **Rh-Antibodies**
      - **→ Rh-Antibodies** Cross the placenta
      - → Enter fetal bloodstream → Attack fetal RBC's → **Hemolytic Anemia**
    - § **Note:** You can prevent an Rh-Negative mother from being sensitized by administering Rh-Immunoglobulin (aka: Anti-D-Antibodies) at strategic times during the pregnancy

Mother's Rh factor	Father's Rh factor	Baby's Rh factor	Precautions
Rh positive	Rh positive	Rh positive	None
Rh negative	Rh negative	Rh negative	None
Rh positive	Rh negative	Could be Rh positive or Rh negative	None
Rh negative	Rh positive	Could be Rh positive or Rh negative	Rh immune globulin injections



BLOOD GROUP ANTIBODIES:

- **Anti-A / Anti-B Antibodies:**
  - **Are Naturally-Occurring Antibodies:**
    - Ie: Present at birth
    - Ie: Do not require an immune-sensitizing event
  - **Are Immunoglobulins of *type:***
    - IgM type antibodies
  - **Are Present In *plasma* of people who lack the corresponding Antigen**
    - Eg: A-type individual will have 'Anti-B' Antibodies (against B-Antigens)
    - Eg: B-Type individual will have 'Anti-A' Antibodies (against A-Antigens)
    - Eg: O-type individual will have 'Anti-A' & 'Anti-B' Antibodies
  - **If Antibodies contact their respective Antigen, A Haemolytic Reaction may occur**
  - **Clinical significance:**
    - Determines a patient's ABO-compatibility when receiving transfusions

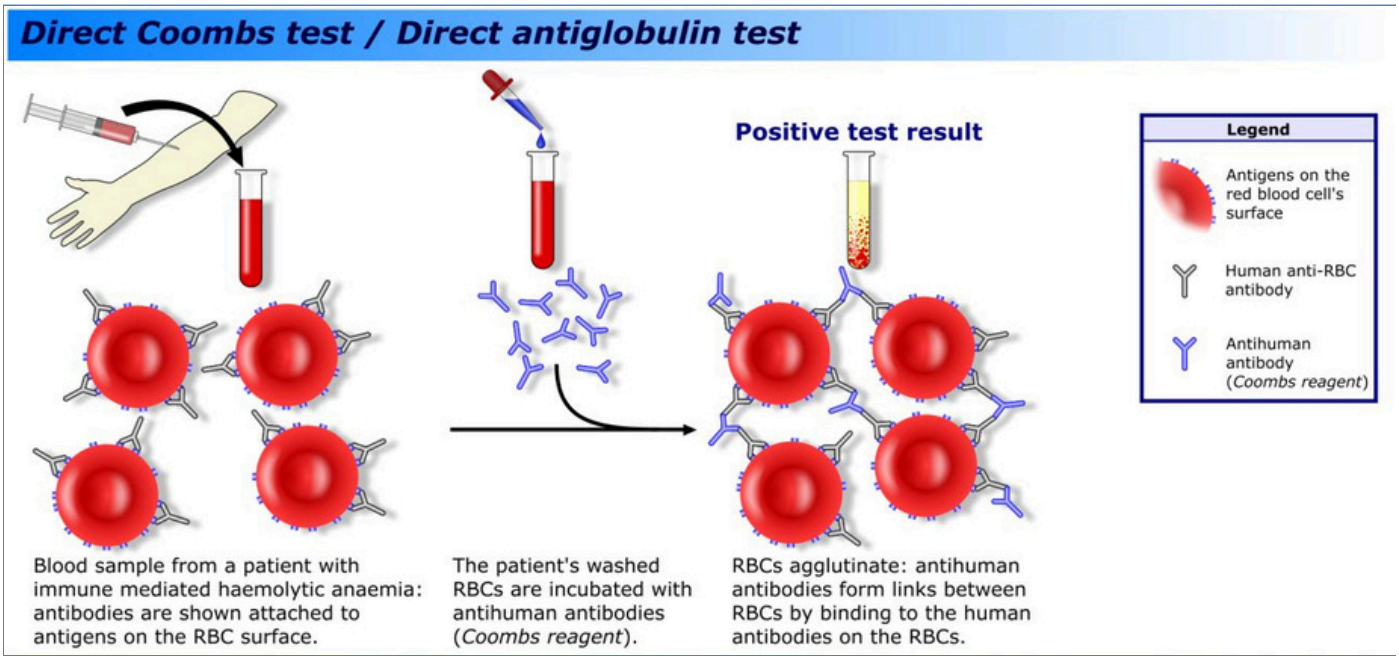


- **Anti-D Antibodies:**
  - **Are Immune Antibodies:**
    - Ie: Produced following an immune-sensitizing event
      - Eg: Via transfusion ...or
      - Eg: Trans-Placental Passage
  - **Are Immunoglobulins of *type:***
    - IgG type antibodies
    - Note: Only IgG-Ab's are capable of trans-placental passage
  - **Most Important IgG = the 'Rh-Antibody' (Anti-D)**
  - **Clinical Significance:**
    - Determines a foetus' risk of Haemolytic Disease of the Newborn
    - Determines a patient's absolute ability to receive a Rh-Positive transfusion

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



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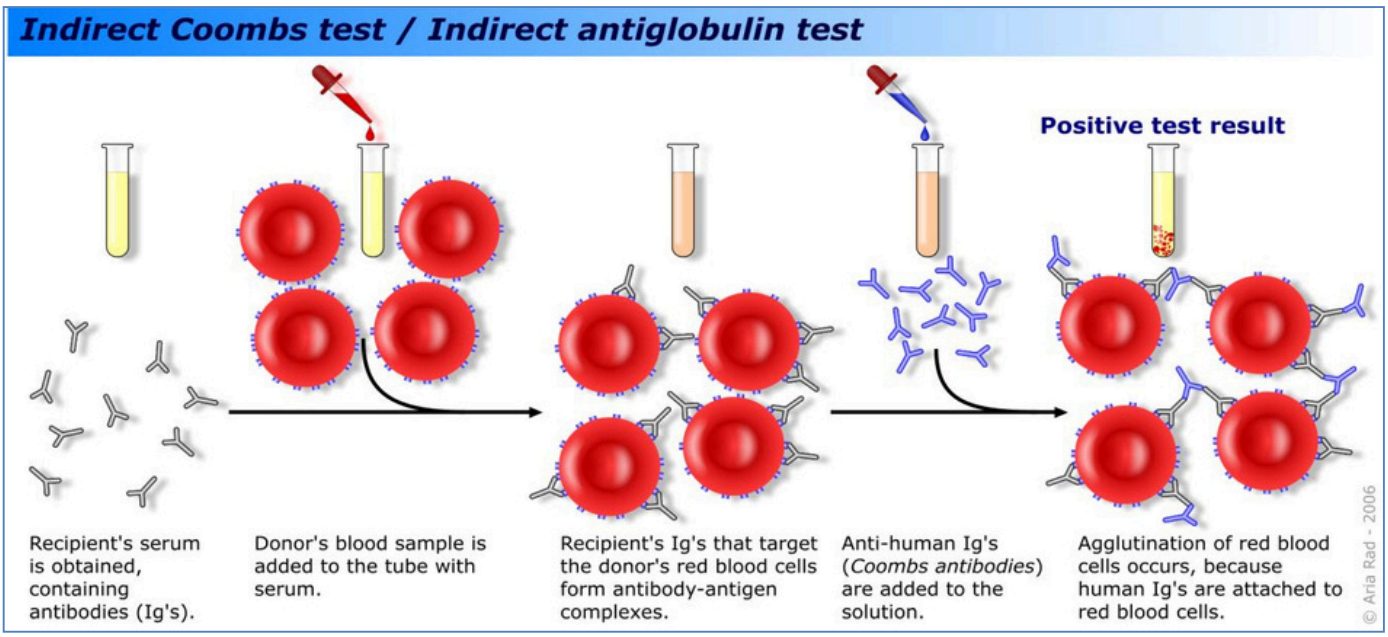
  - **Indirect (IDAT):**
    - § Detects antibodies against RBCs present in the patient's serum
    - § Serum is extracted from the blood, and is incubated with RBCs of known antigenicity
    - § If agglutination occurs, the indirect Coombs test is positive
    - § It is used to detect very low concentrations of antibodies present in a patient's
    - § plasm a/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*



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BLOOD DONATION PROCESS:

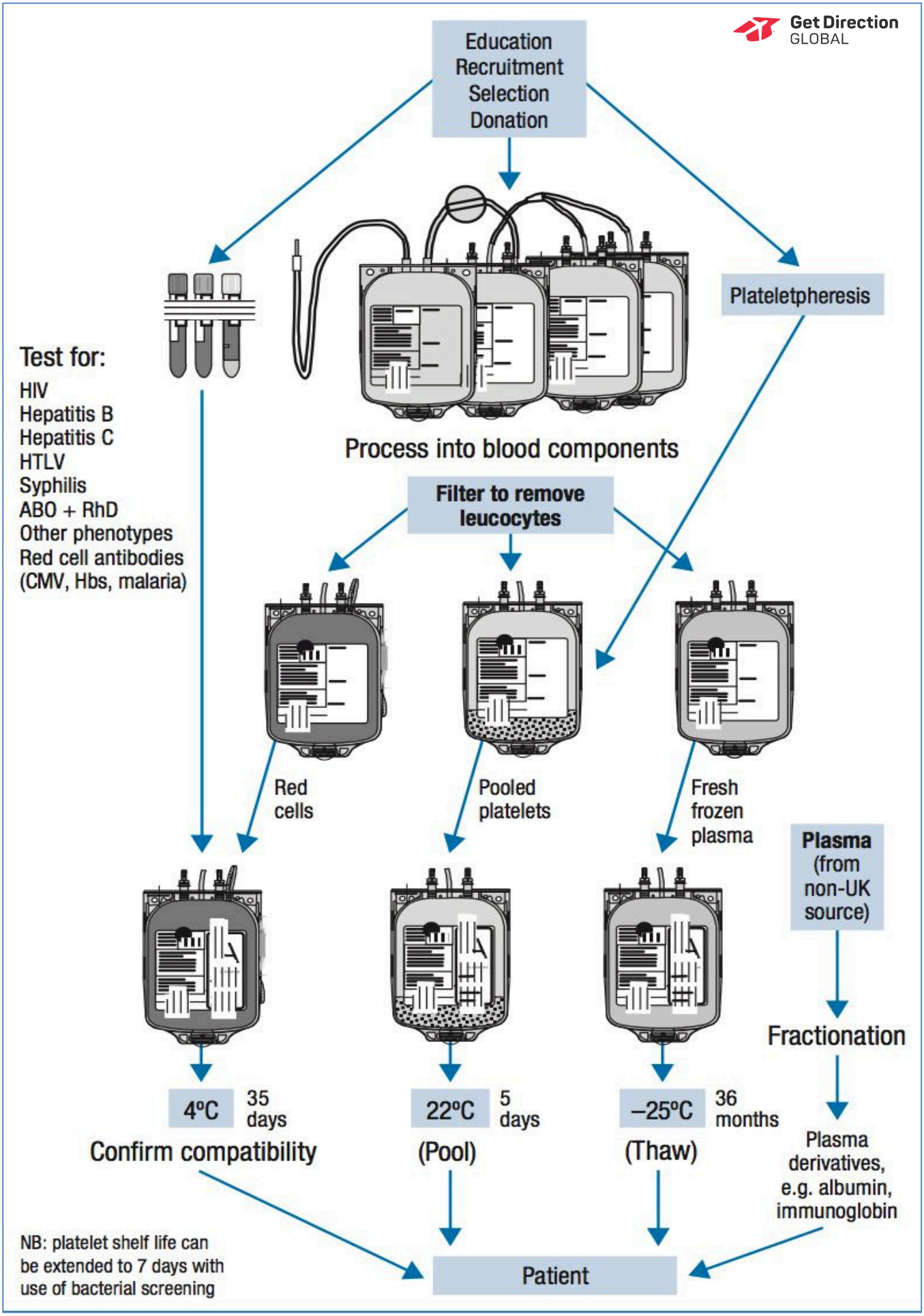
- **1- Blood Donation:**
  - Donors carefully selected:
    - Healthy
    - 18-65yrs
    - Minimum Hb Level (not anaemic)
    - No infection
    - No Meds/Drugs
  - Frequency: 2-3times/year
  - Volume: 450mL (A *Pint*)
- **2- Collection:**
  - Can be stored for 5-6 weeks
  - Stored in PVC Bags:
  - With 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 crystalize 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)

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 O2 Delivery to Tissues***
    - Expect a rise of *10g/L* of Haemoglobin *Per Unit of Blood (450mL)*

      Egs of Eligible 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

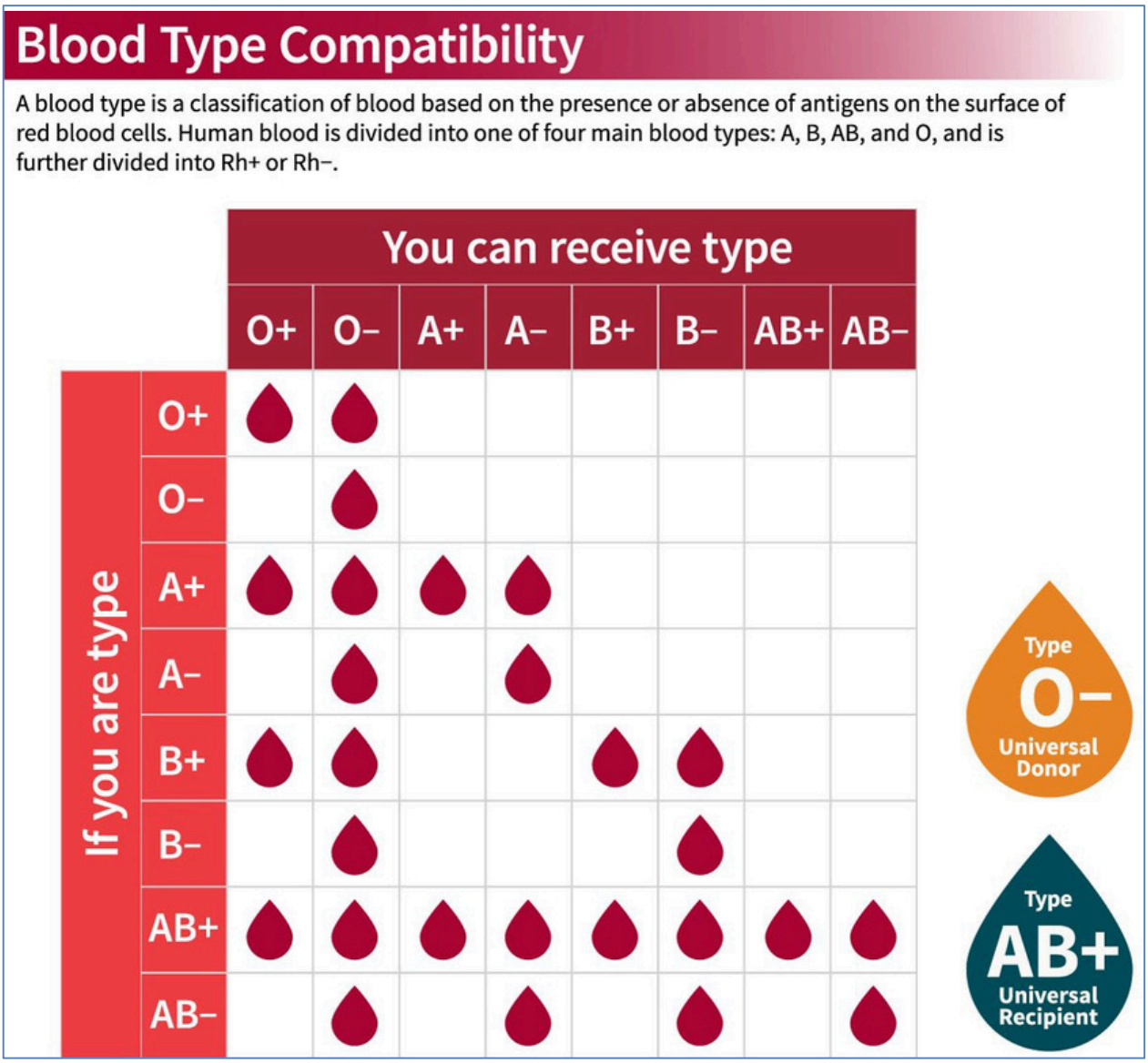
      Factor IX & Prothrombin:
      - Treatment of Factor IX Deficiency
      - Treatment of Christmas Disease
- **Cryosupernatant:**
  - Albumin
  - Immunoglobulins
  - **Reasons For Transfusion:**
    - Used as 'Volume Expanders' – in Hypovolemic Shock
    - **Albumin:**
      - Volume Expander
      - To Treat Hypoalbuminaemia – Eg: Burns/Renal Patients
    - **Immunoglobulins:**
      - Treatment of Immunocompromised Patients



https://www.transfusionguidelines.org/transfusion-handbook/3-providing-safe-blood/3-3-blood-products

BLOOD TRANSFUSIONS:

- **What is it?**
  - o Involves the infusion of blood from a donor to a recipient
  - o Compatibility between *Donor RBC Antigens* & *Recipient Plasma Antibodies* Essential
  - o If incompatible – haemolytic reaction may occur
- **Universal Donor:**
  - o O-Negative
    - § No A or B Antigens
    - § No Rh-D Antigens
- **Universal Recipient:**
  - o AB-Positive
    - § No anti-A or anti-B Antibodies
    - § No anti-Rh-D Antibodies
- **Group Specific Blood Vs Cross Matched Blood:**
  - o **Group Specific =** Blood of any 'Type' (ABO,Rh) that's compatible with the Recipient (20mins)
  - o **Cross Matched =** Complex Pre-Transfusion Testing for Compatibility across *all* Blood Types (1hr)
- **In Emergency Situations:**
  - o In emergencies, there's often no time to do a blood group or do a full cross match, so O-Neg is given



https://stanfordbloodcenter.org/donate-blood/blood-donation-facts/blood-types/0318-southbay-center-infographics_compatibility-web/

COMPLICATIONS OF BLOOD TRANSFUSION:

- **Immediate Complications:**
  - o **Immunological:**
    - § **Haemolytic Reaction -** Fever, Tachycardia, Hypotension, Shock
      - Reaction → Intravascular Haemolysis
      - Ie: Rapid Destruction of RBCs → Reduced O2-Carrying Capacity
        - o Involving ABO Antibodies = Life threatening
        - o 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)

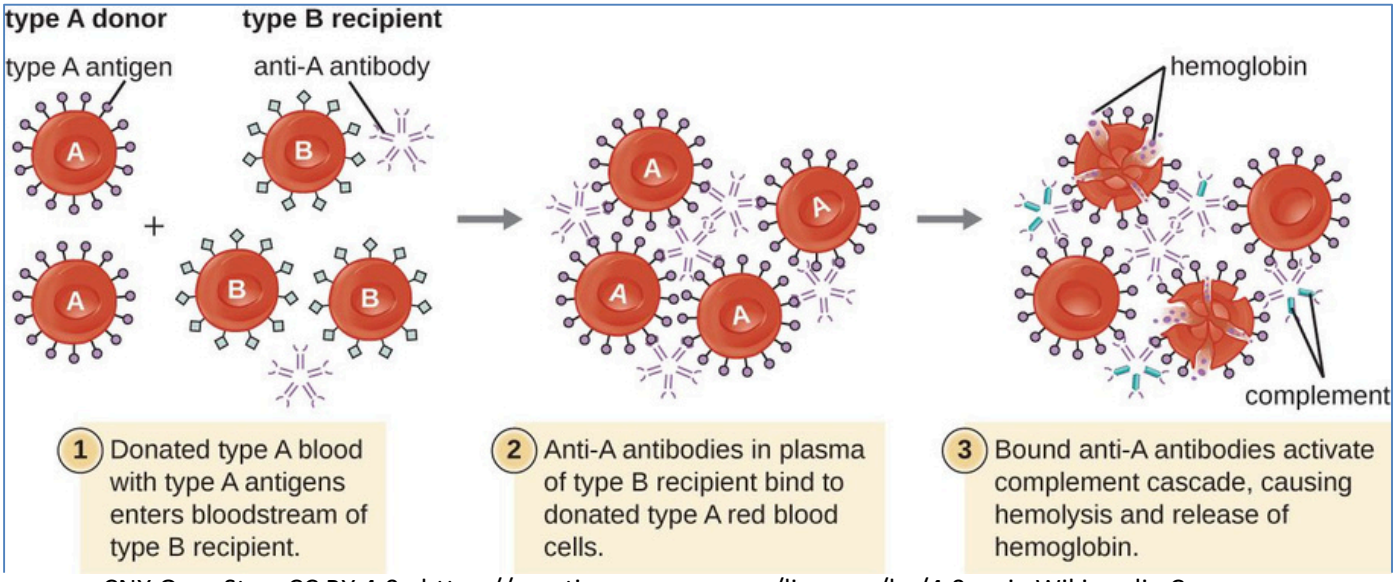
      Allergic Reactions
      - Triggered by IgE Antibodies (covered more in 4th year)
      - May result in Anaphylactic Shock

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

- **Delayed Complications:**
  - o **Immunological:**
    - § **Delayed Hemolytic Reactions**
    - § **Alloimmunisation** - 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

  - o **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



ANAEMIAS

ANAEMIAS

Get Direction GLOBAL

General:

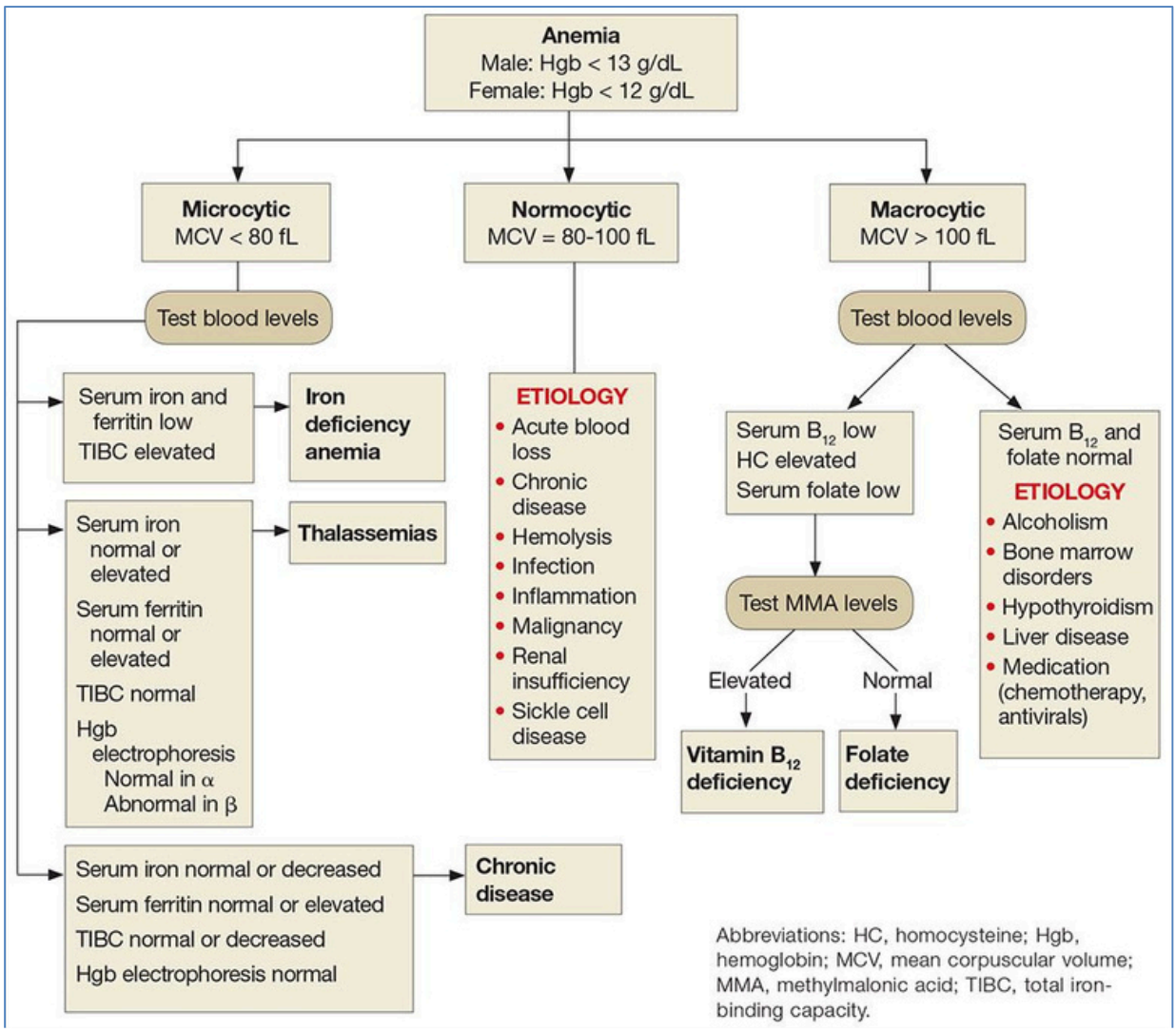
- **Definition = "Decreased haemoglobin concentration in blood"**
  - o May be Low Hb
  - o OR low Haematocrit/Packed Cell Volume
  - o Anaemia = generally less than 100g/L
- **Normal Hb Range:**
  - o (Normal Hb Concentration depends on age/sex/geographical location)
  - o 13 - 16g/dl (male) (130-160g/L)
  - o 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** (Haemolytic/Microangiopathy/G6PD/Sickle/Thalassaemia/Spherocytosis)
- **Spurious** (Increased Plasma Volume – Eg: Pregnancy/Fluid Overload)

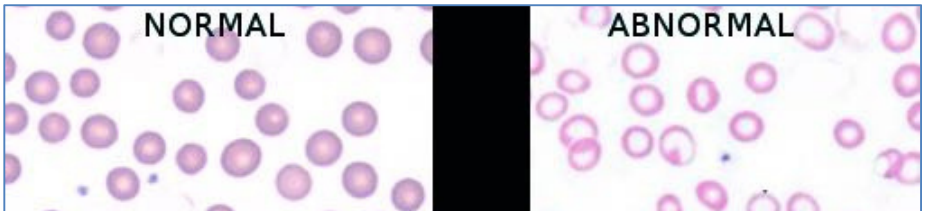
M orphologies:

- **Size Classifications:**
  - o **Microcytic:** Small - Reduced MCV
  - o **Normocytic:** Normal MCV
  - o **Macrocytic:** Large – Increased MCV
- **Staining/Colour:**
  - o Normal RBCs stain well – **(Normochromic)**
  - o Anaemic cells stain lightly - **(Hypochromic)**

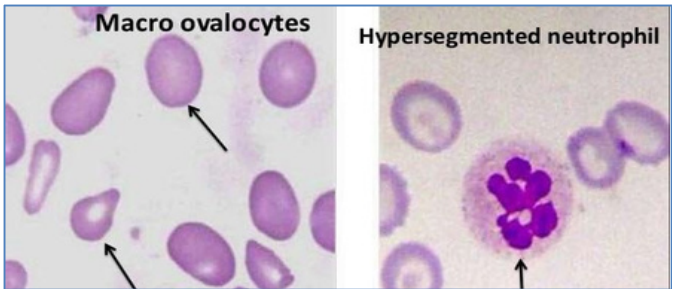


M icroscopy (Blood Film s):

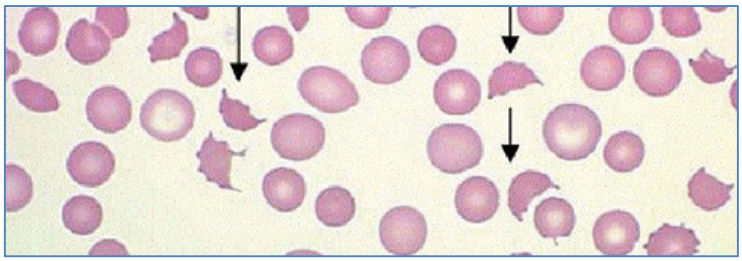
- **Iron Deficiency Anaemia:**
  - o Hypochromic RBCs - Increased Central Pallor
  - o Microcytic
  - o Pencil Cells (RBCs with a single sharp edge)



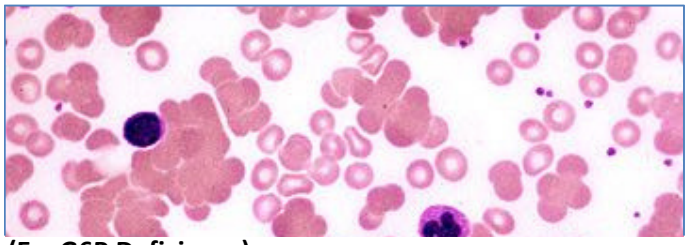
- **M egaloblastic Anaem ia:**
  - o Oval Macrocytic RBCs
  - o Hypersegmented Neutrophils
  - o Normochromic



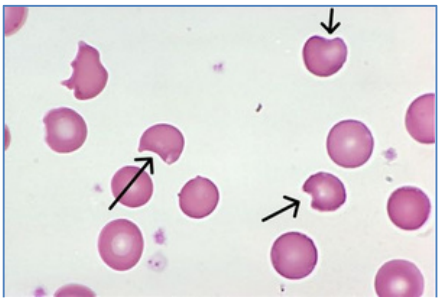
- **Warm Antibody (IgG) Autoimmune Haemolytic Anaemia:**
  - o Microspherocytes (Small, RBCs with No Central Pallor)
  - o Evidence of Haemolysis (Reticulocytes, Nucleated RBCs, Schistocytes)



- **Cold Antibody (IgM) Autoimmune Haemolytic Anaemia:**
  - o Agglutination of RBCs (Ugly clumping of) @ <20oC
  - o May agglutinate in peripheries @ cold temperatures →Raynaud's Phenomenon

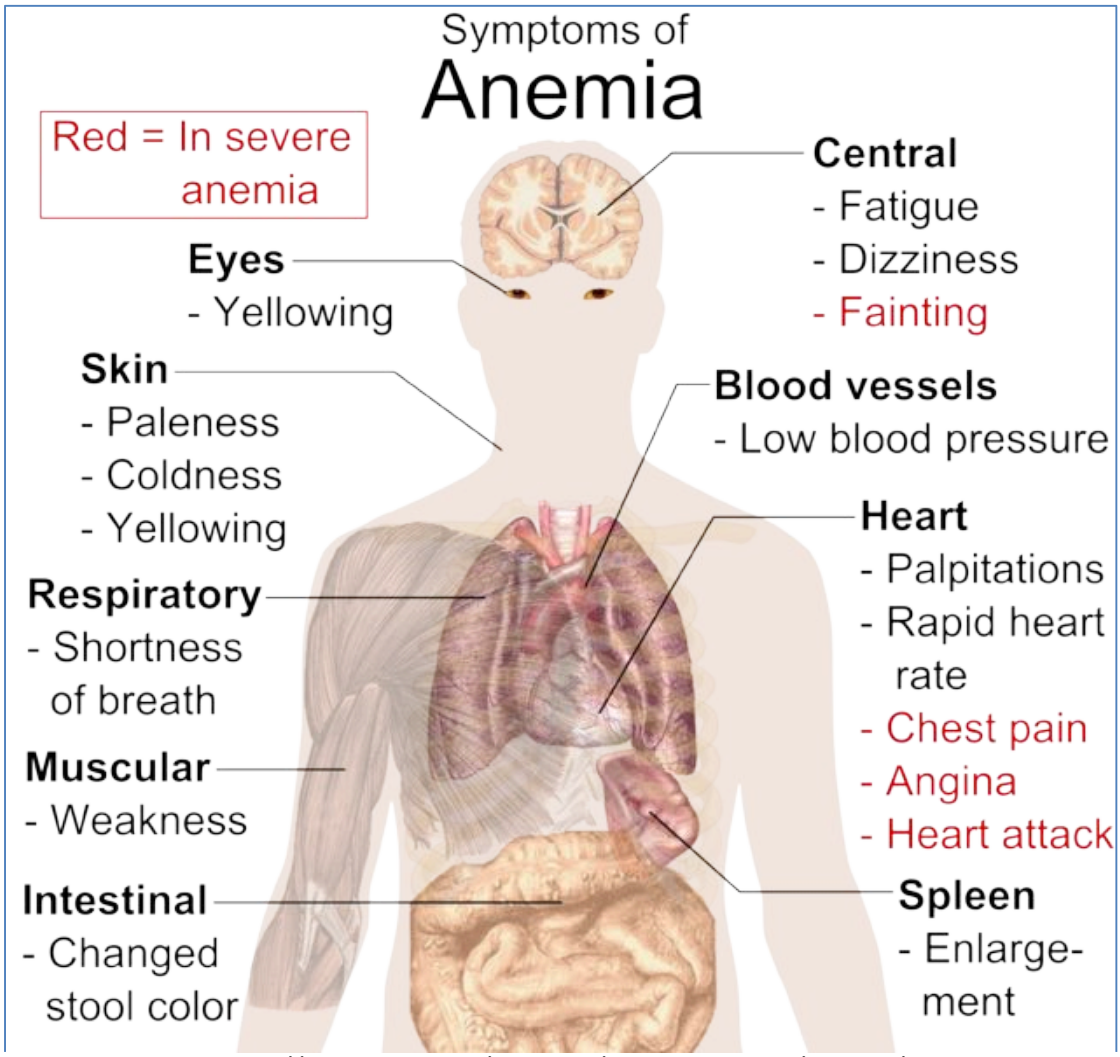


- **Oxidative Haemolysis (Eg: G6P Deficiency):**
  - o (Affects cell fluidity, Hb Condenses)
  - o Bite Cells (RBCs) – Macrophages take bites out of RBCs
    - § Note: an Indication for Splenectomy
  - o Blister Cells (RBCs)
  - o Irregularly contracted microspherocytes



Clinical Features of Anaemia:

- May be Asymptomatic
- **General Anaemia Symptoms:**
  - o o Fatigue, Headaches & Faintness
  - o Intermittent Claudication
    Exertional Dyspnoea
    Exertional Angina
- **General Anaemia Signs:**
  - o Pallor (Mucosal/Facial/Palmar Crease)
  - o Tachycardia
  - o Systolic Flow Murmur (Hyperdynamic Circulation)
  - o Cardiac Failure
- **Some Signs Specific to Different *Types* of Anaemia:**
  - o o Koilonychia (Spoon-shaped nails) – Iron Deficiency
  - o Glossitis – Iron/B12 Deficiency
    Jaundice – Haemolytic Anaemia o Splenomegaly – Haemolytic Anaemia, Leukaemia, Lymphoma o Bone Pain/Deformities – Thalassemia Major, Myeloma
  - o Leg Ulcers – Sickle Cell



https://www.phlbi.org/divisions/blood-disorders/anemia/

Investigations:

- **Mean Cell Haemoglobin Concentration (MCHC):**
  - o The average *concentration of haemoglobin in a given volume of blood*
  - o Derived from the measurement of haemoglobin and the haematocrit
    - § Haemoglobin value = amount of haemoglobin in a volume of blood while the haematocrit is the ratio of the volume of red cells to the volume of whole blood) The normal range for the MCHC is 32 - 36%
- **Mean Cell Haemoglobin (MCH):**
  - o The average *amount of haemoglobin in the average RBC*
  - o 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)
  - o The normal range for the MCH is 27 - 32 picograms
- **Mean Cell Volume (MCV):**
  - o Average size of RBC
  - o Described as:
    - § Microcytic (smaller than normal)
    - § Normal
    - § Macrocytic (larger than normal)

Differential Diagnosis of Anaemia Based On MCV			
Hypochromic Microcytic (MCV <80)	**Normochromic Normocytic (80<MCV<100)**		**Macrocytic (MCV>100)**
Fe Deficiency Thalassemia Lead Poisoning Sideroblastic Anemia Chronic disease (Some cases)	**Low Reticulocytes:** Myelodysplasia Infiltration (leukemia, myeloma, mets, infection) Myelofibrosis Aplasia Chronic disease (some cases) Liver disease Uremia Hyper/hypo-thyroid Addison's disease	**High Reticulocytes** Hemolytic anemia Post-hemorrhagic anemia Treated nutritional deficiency	Megaloblastic (B12, Folate, Drugs) Myelodysplasia Liver disease Alcohol Reticulocytes

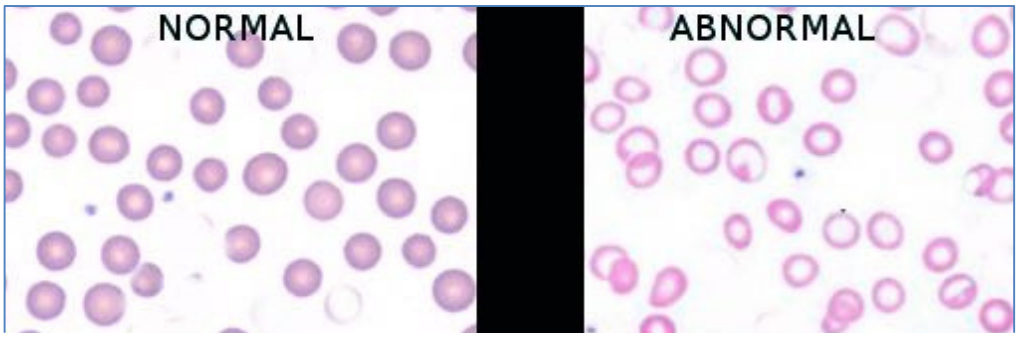
- **Iron Studies Interpretation:**

Condition	MCV	Iron	Ferritin	TIBC	Transferrin	Transferrin saturation
Iron deficiency	↓	↓	↓	↑	↑	↓
Inflammatory anaemia	↔	↓	↑	↓	↓	↓
Thalassaemia minor	↓	↔	↔	↔	↔	↔
Thalassaemia major	↓	↔/↑	↑	↓	↓	↑
Sideroblastic anaemia	↓	↑	↑	↔	↔/↑	↑
Iron overload	↔	↑	↑	↓	↓	↑

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/Inflammation Sideroblastic Anaemia Thalassemias A & B Lead Poisoning	Iron Studies, Fe-Binding, Ferritin Blood Film (Pencil Cells = IDA)
Anaemia **High MCV (Macrocytic/ Megaloblastic)**	Megaloblastic (B12/Folate Deficiency) - Eg: Pernicious Anaemia - Eg: Coeliac Disease/Short bowel 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**	Acute Blood Loss 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 Renal Failure Pregnancy (Spurious)	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

IRON DEFICIENCY ANAEMIA (Microcytic):

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



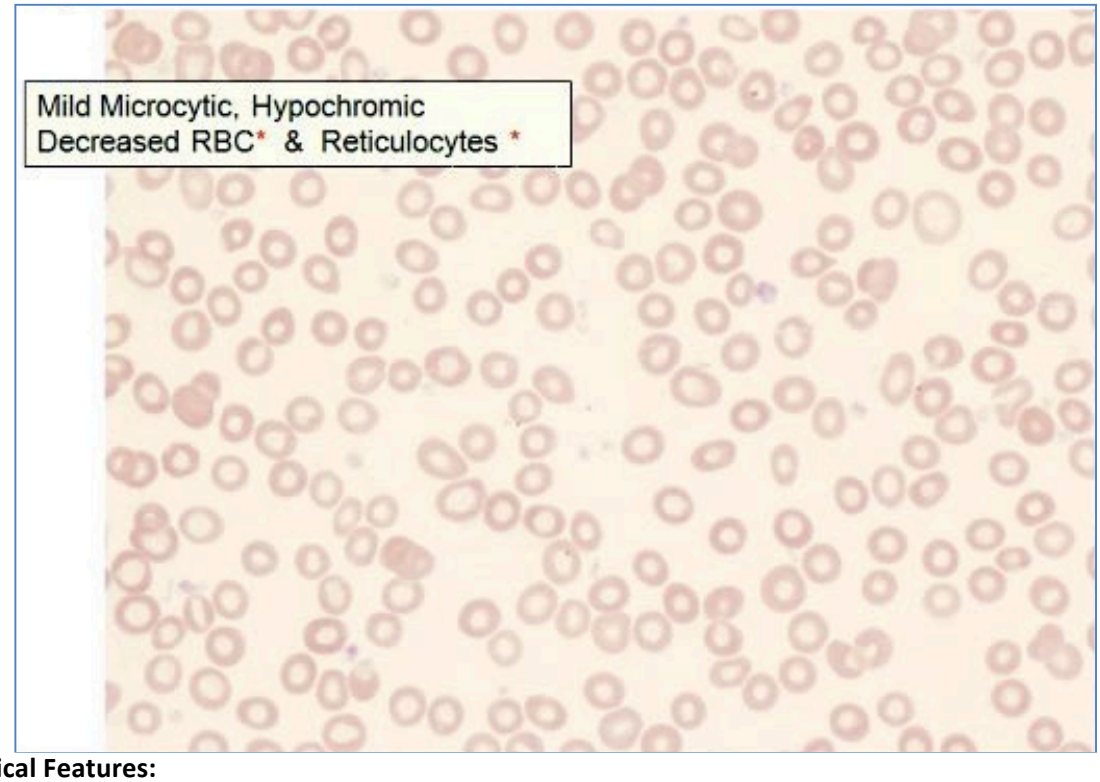
- **Clinical Features:**
  - o **Symptoms & Signs:**
    - § **General Anaemia Symptoms:**
      - Fatigue, Headaches & Faintness
      - Exertional Dyspnoea
      - Exertional Angina
      - Intermittent Claudication
      - (Incl: Exacerbations of CVS/Resp problems in Elderly – Eg: Claudication & Angina)
    - § **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 Chelitis/Stomatitis**
      - ***Koilonychia (Spoon Nails)**
      - ** Brittle Nails, Brittle Hair*
  - o **Diagnosis:**
    - § **Blood Count & Film** (Microcytic, Hypochromic, Poikylocytosis, Anisocytosis, Pencils)
    - § **Iron Studies** (↓Ferritin;↓Iron; ↑TIBC)
  - o **Differentials (for low MCV):**
    - § Thalassaemia
    - § Anaemia of Chronic Disease
    - § Sideroblastic Anaemia (Very Rare)
  - o **Treatment:**
    - § Iron Supplementation

ANAEMIA OF CHRONIC *Inflammatory* DISEASE (Microcytic/Normocytic):

- **Aetiology:**
  - **Chronic Infection** (Eg: Tuberculosis)
  - **Chronic Inflammatory Disease** (Eg: Crohn's/Rh Arthritis/SLE/Malignancy)
- **Pathogenesis:**
  - **Chronic Infection/Inflammation →**
    - ↓RBC Survival → RBC Death outpaces RBC production → Anaemia
    - ↓EPO Release → Reduced Stimulus for Erythropoiesis
    - ↓Iron Transfer/Release from Macrophages in Bone Marrow → Functional iron deficiency →

Morphology: Anaemia

-
  - Typically Normocytic (Sometimes Microcytic) [Debatable]
  - Hypochromic
  - Fewer RBCs



- **Clinical Features:**
  - **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)

THALASSAEMIAS:

- **Aetiology:**
  - o Genetic mutation/deletion in the Alpha or Beta Globin genes for Haemoglobin
  - o **Alpha Thalassaemia:**
    - § Deletion of 1/more of the 4 Alpha Globin genes
  - o **Beta Thalassaemia:**
    - § Mutations in the Beta Globin genes – prevent B-chain formation
- **Pathogenesis:**
  - o ↓ Synthesis of Alpha/Beta Globin chains – Haemoglobin Disorder - Ineffective erythropoiesis
  - o ↑ Haemolysis – due to aggregation of unmatched globin chains
- **Microscopy:**
- o May exhibit *Poikylocytosis* (RBCs – weird shapes/sizes)

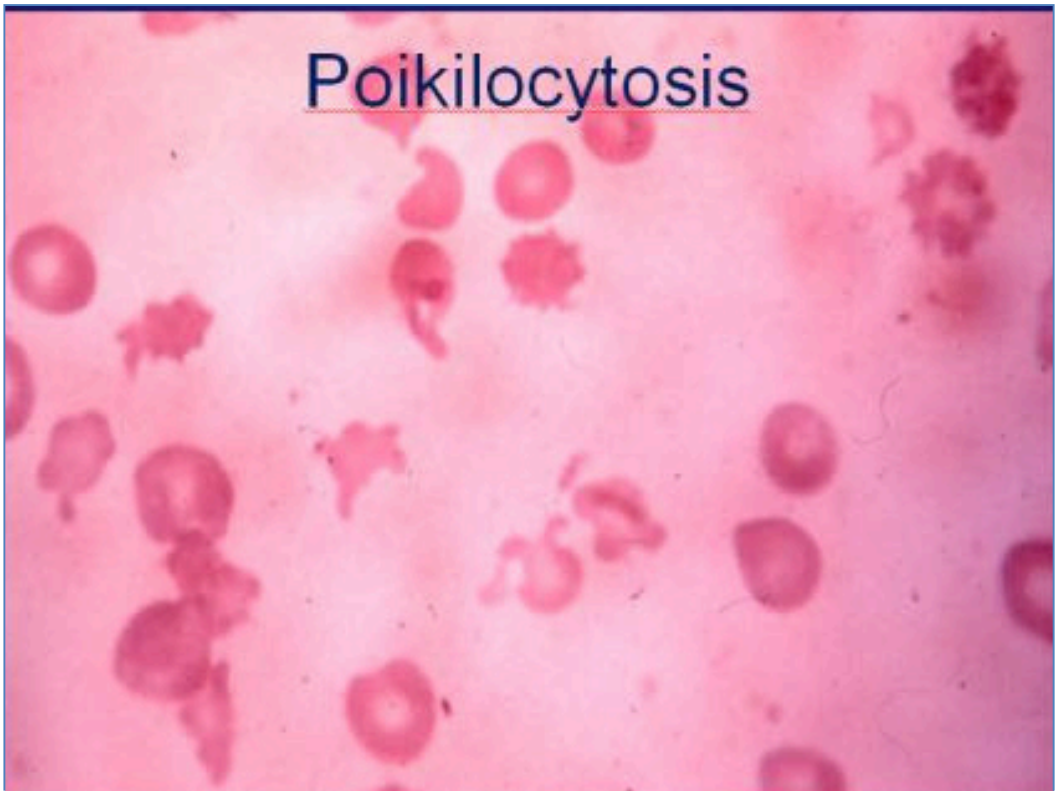
Clinical Features:

- o May be mild → Minimal symptoms / No treatment required
- o May be more severe → Typical anaemia-type symptoms
  - § Eg: Fatigue, weakness
  - § Eg: Jaundice/Dark urine

- **Treatment:**
- o Severe forms may require regular blood transfusions

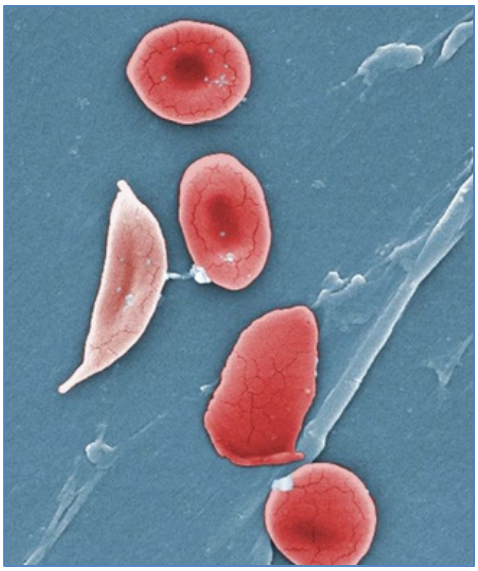
Complications:

- o Iron Overload (Eg: From frequent blood transfusions) → Damage to heart/liver/endocrine organs
- o Infection (Especially post splenectomy)
- o Bone Deformities (Thalassemia can cause physical bone marrow expansion → abnormal bone structure; especially in face and skull)
- o Splenomegaly (May require splenectomy)
- o Slowed growth & delayed puberty
- o Congestive heart failure



SICKLE CELL ANAEMIA:

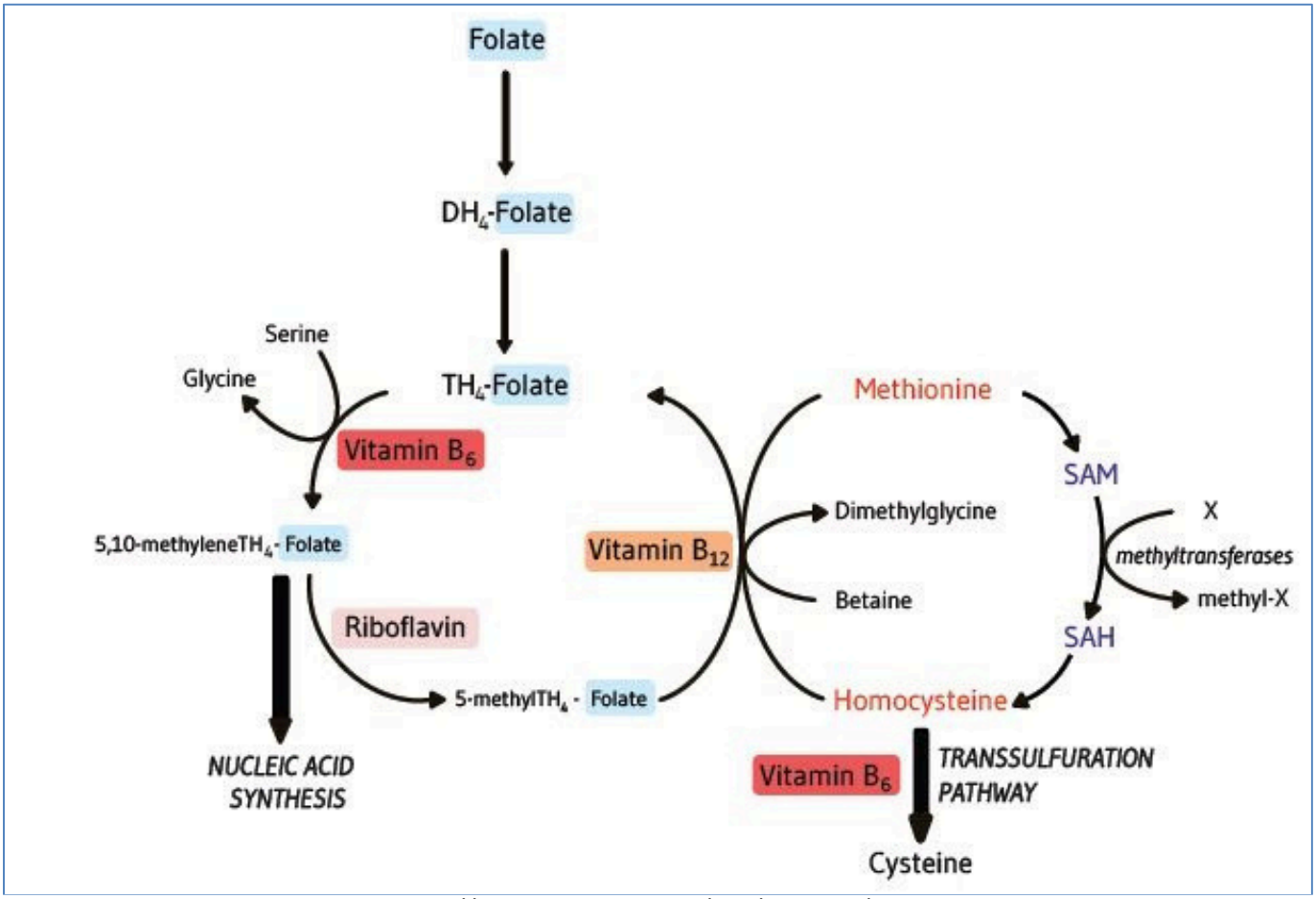
- **Aetiology:**
  - Inherited genetically
  - Prevalent in Afro-Caribbean populations
- **Pathogenesis:**
  - Abnormal Beta-Haemoglobin Chain →
    - Abnormal Hb – Insoluble – Forms crystals @ low O2 Tension
    - Leads to sickle-shaped RBC → RBCs are rigid, sticky & get stuck in blood vessels
    - RBCs Clog small capillaries → Tissue Necrosis
    - Episodes of haemolysis → Further anaemia
- **Microscopy:**
  - sickle-shaped RBCs
- **Clinical Features:**
  - Episodes of Haemolysis
  - Anaemia Symptoms
  - ***Episodes of Pain ('Pain crises'):**
    - Due to microangiopathic blockages due to sickle cells → tissue hypoxia/ischaemia → Pain
    - → Chest/Abdo/Joint/Bone pains
    - 'Pain crises' may occur infrequently, or many times a year
  - Swelling of hands and feet
  - Frequent infections
  - Delayed growth/puberty
- **Treatment:**
  - Currently no cure; But Stem cell transplants have future promise
  - Treatment aimed at avoiding pain, relieving symptoms & preventing complications
  - **Hydroxyurea –** reduces frequency of painful crises
  - **L-Glutamine** – Reduces frequency & severity of pain crises
  - **Analgesics**
- **Complications:**
  - Retinopathy
  - Growth delay
  - Renal disease
  - Stroke
  - Pulmonary hypertension
  - Heart disease
  - Leg ulcers
  - Priapism
  - Gallstones
  - Increased risk of miscarriage



MACROCYTIC ANAEMIA:

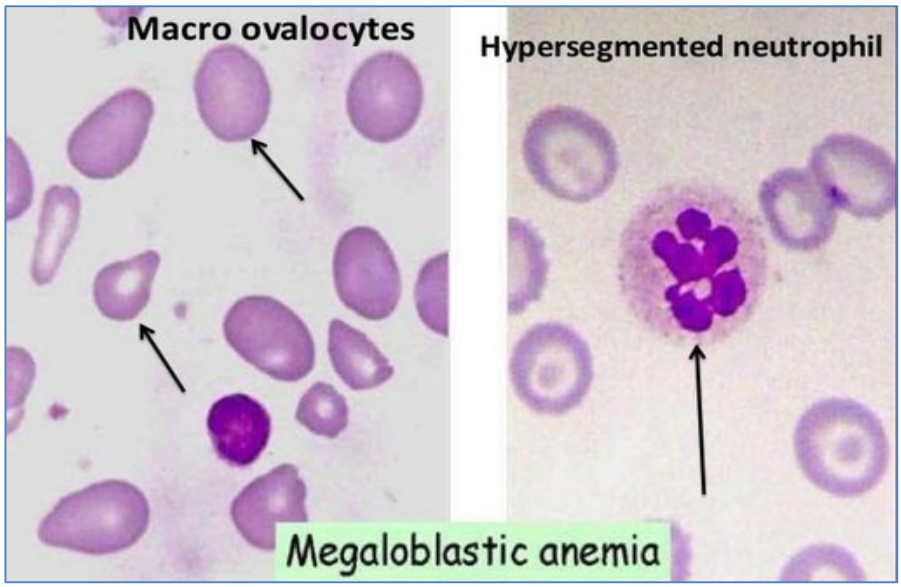
- (2nd most common type of anaemia)
- ("Megaloblasts" = *large, Erythroblasts with Immature Nuclei* - seen in the Marrow)
- **Aetiologies:**
  - **VitB12 Deficiency; Possible causes:**
    - ****Malnutrition** – Lack of VB12 Dietary Intake
    - **Gastric** – Deficiency of ***Intrinsic Factor*** (Eg: **Pernicious Anaemia** – autoimmune response to parietal cells of stomach → ↓ IF → ↓ VitB12 Absorption)
    - **Intestinal –** Eg: Resected Ileum/Crohn's Disease
  - **Folate Deficiency; Possible causes:**
    - ****Malnutrition** – 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 General Causes:**
    - ****Alcoholism (or Liver Disease)**
    - **Cytotoxic Chemo Drugs (Eg: Methotrexate)**
    - **Old Age**

- **Pathogenesis:**
  - VitB12/Folate are Necessary for Nuclear DNA Synthesis
  - → defective nuclear maturation of erythroblasts
  - → Reduced RBC Production



https://lpi.oregonstate.edu/mic/vitamins/folate

- **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"** (Bigger, Blueish RBCs)
      - **Some Nucleated RBCs**
    - **+ An-Isocytosis** (variations in size)
    - **+ Poikylocytosis** (Variations in shape)



- **Clinical Features:**
  - **General Anaemia Symptoms & Signs**
  - **Signs & Symptoms Specific to Megaloblastic Anaemia:**
    - Glossitis (Red Sore Tongue)
    - Angular Stomatitis/Chelitis
    - Peripheral Neuropathy (Paraesthesia, ↓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)**

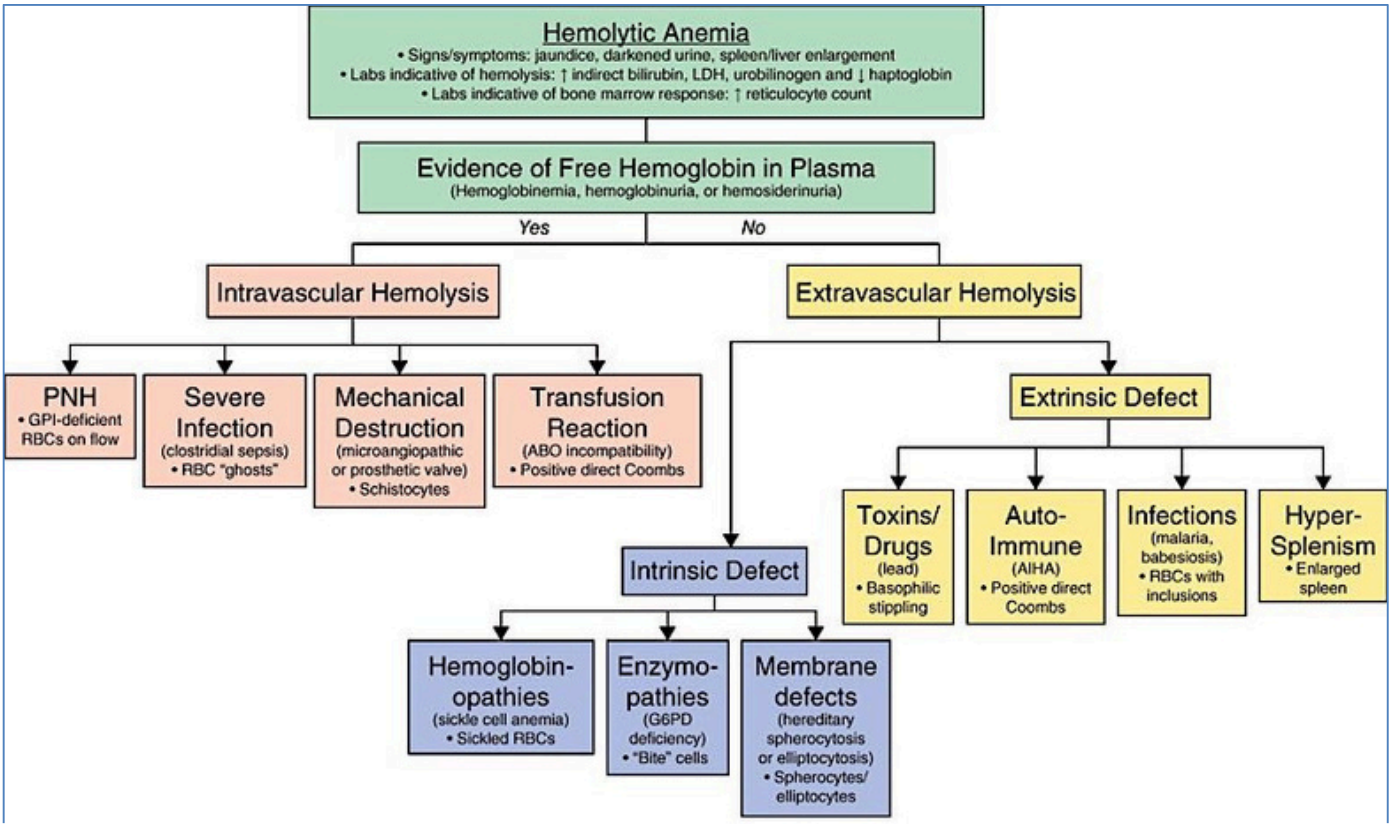
"HA" - HAEMOLYTIC ANAEMIA:

- **What is it?**
- o Anaemia due to Increased/Abnormal/Premature RBC Destruction

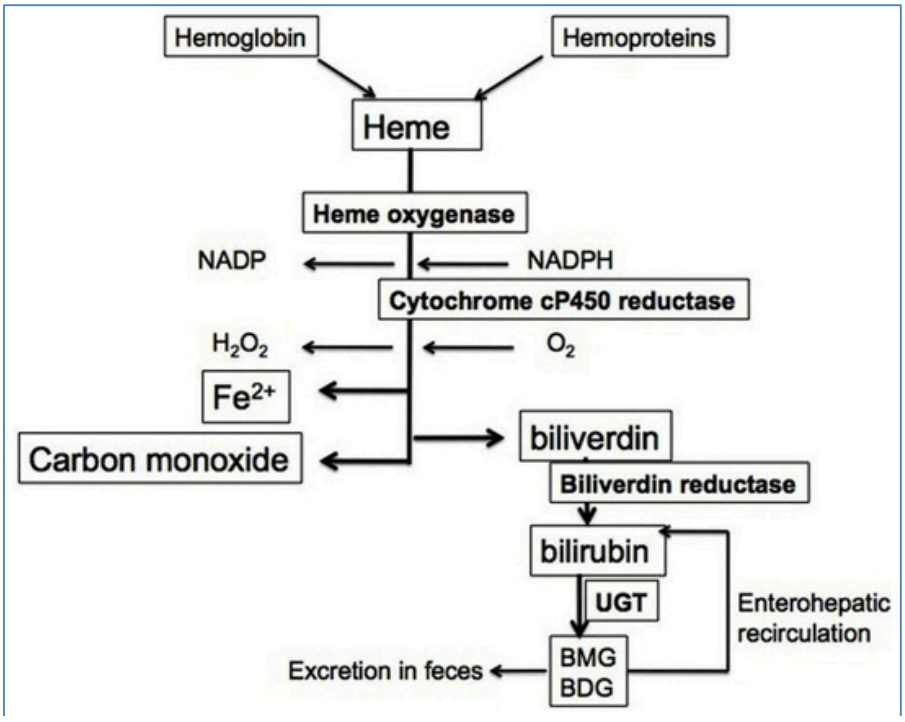
Aetiologies (See Flowchart Below):

o **Intravascular Haemolysis:** Occurs within the ***Circulation***

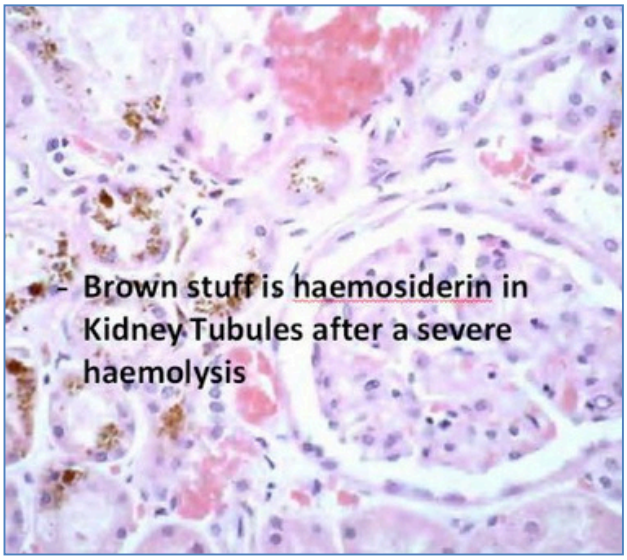
o **Extravascular Haemolysis:** Occurs in the ***Reticuloendothelial System*** (Liver/Spleen/Marrow)



- **Pathogenesis:**
- o **Breakdown of RBCs due to any cause → Release of *Free Haemoglobin* in Plasma**
  - § **→ Heme Molecule → *Protoporphyrin* & *Iron***
  - § **→ Protoporphyrin → Excess Bilirubin →↑Bilirubin (Unconjugated)→ Jaundice**
  - § **→ Bilirubin Conjugated in Liver** → Excreted in Bile & Faeces



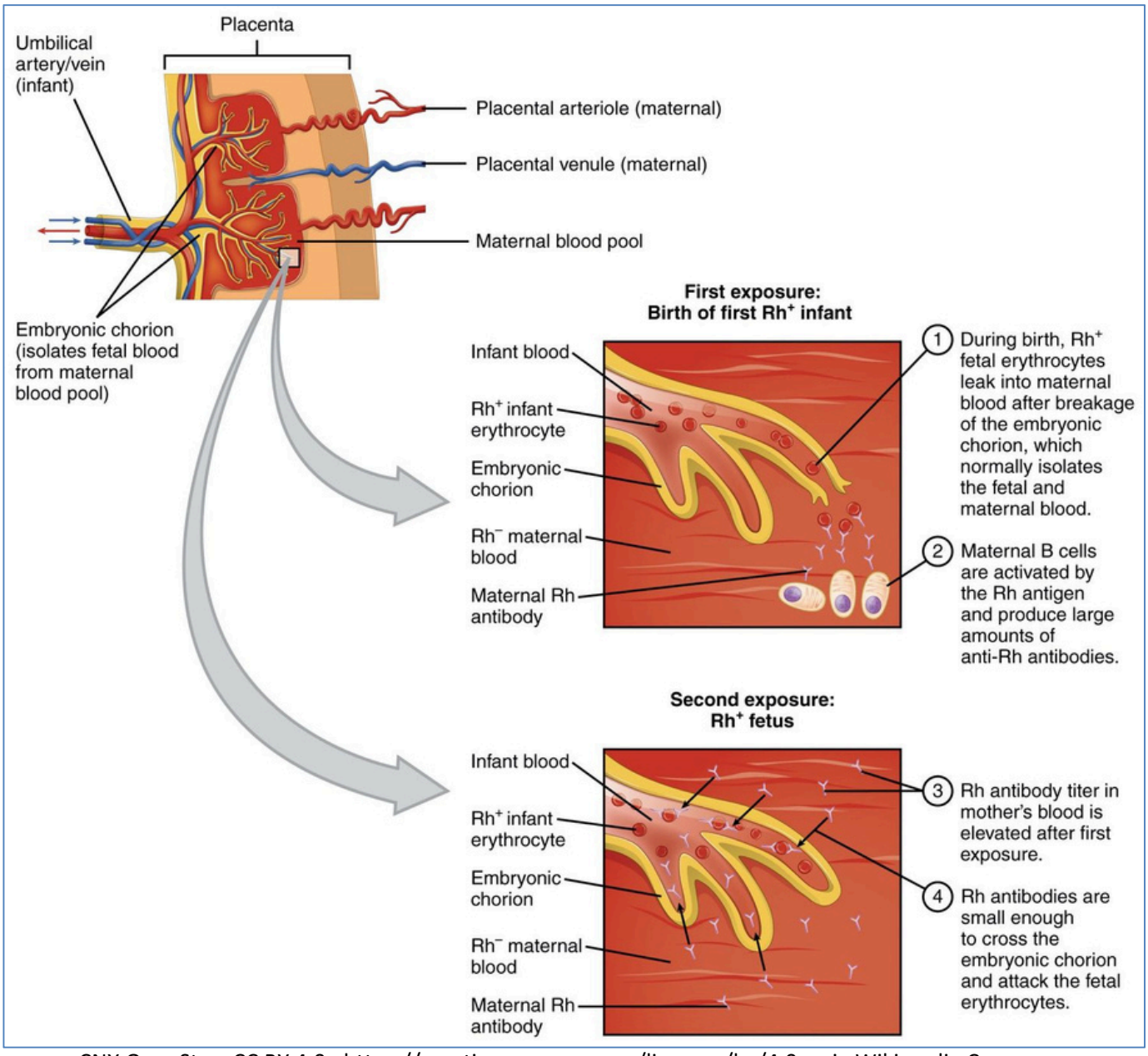
- **Clinical Features:**
  - **Symptoms:**
    - **General Anaemic Symptoms & Signs +**
    - **Symptoms Specific to Haemolytic Anaemia:**
      - Jaundice (Mild & Fluctuating)
      - Splenomegaly
      - Pigment Gall Stones (If Chronic HA)
      - Venous Stasis Ankle Ulcers (Sickle Cell)
      - Microangiopathy/Infarction/Raynaud's
  - **Laboratory Evaluation:**
    - **Hb –** Low
    - **Reticulocytes –** Elevated
    - **Elevated Free-Hb** in Blood (*Haemoglobinaemia*)
    - **Hb in Urine** (*Haemoglobinuria*) → Red-Brown Urine
    - **Haemosiderin** (iron from Hb) in Urine (*Haemosiderinuria*)
    - **LFTs – (**↑Bilirubin, ↓ Haptoglobins**)**
    - **Blood Smear – (**Broken RBCs, Reticulocytosis, Congenital RBC Disorders, Anaemia)
    - **Coombe's Test – (**?Autoimmune Haemolytic Anaemia**)**
    - **LDH –** Elevated
    - **Bilirubin** – Elevated



- **A 4Q Approach to Diagnosing Haemolytic Anaemias:**
  - **1- Is there ↑ RBC Breakdown?** (Anaemia?/Jaundice?/Urinary Urobilinogen?)
  - **2- Is there ↑ RBC Production?** (Reticulocytes?/↑MCV?/Polychromasia?)
  - **3- Is it *Extravascular* or *Intravascular*?**
    - ***Extravascular* =** (Splenomegaly?)
    - ***Intravascular* =** (↑Plasma Hb?/↓Plasma Haptoglobin?/Haemoglobinuria?)
  - **4- Why is there Haemolysis?**
    - **Is it Autoimmune (WAHA/CAHA)? → +ve *Coomb's Tests***
    - **Is it Congenital (Sickle / Thalassemia / G6PD / Hereditary Spherocytosis)? → *Blood Smear***
    - **Is it Mechanical (Microangiopathy / March Syndrome / DIC) → *Blood Smear***
- **Treatment:**
  - **Treat Underlying Cause**
  - **Plasmapheresis if Autoimmune**
  - **Splenectomy if Hypersplenism/Hereditary Spherocytosis**
  - **Blood Transfusion if Severe**

HAEMOLYTIC DISEASE OF THE NEWBORN:

- **What is it?**
  - o Condition that develops **in a foetus**, when the **Mother's IgG Anti-RhD Antibodies** crosses the placenta →Foetal Circulation
  - o →Attacks the red blood cells in the foetal circulation
  - o The RBC's are broken down and the foetus can develop reticulocytosis and anaemia → Death
- **Pathogenesis:**
  - o **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
  - o **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 → Fetus
    - § 5- Antibodies Attack Fetal RBCs → Hemolysis
    - § 6- Excess Hemolysis may lead to Jaundice (Heme → Bilirubin)

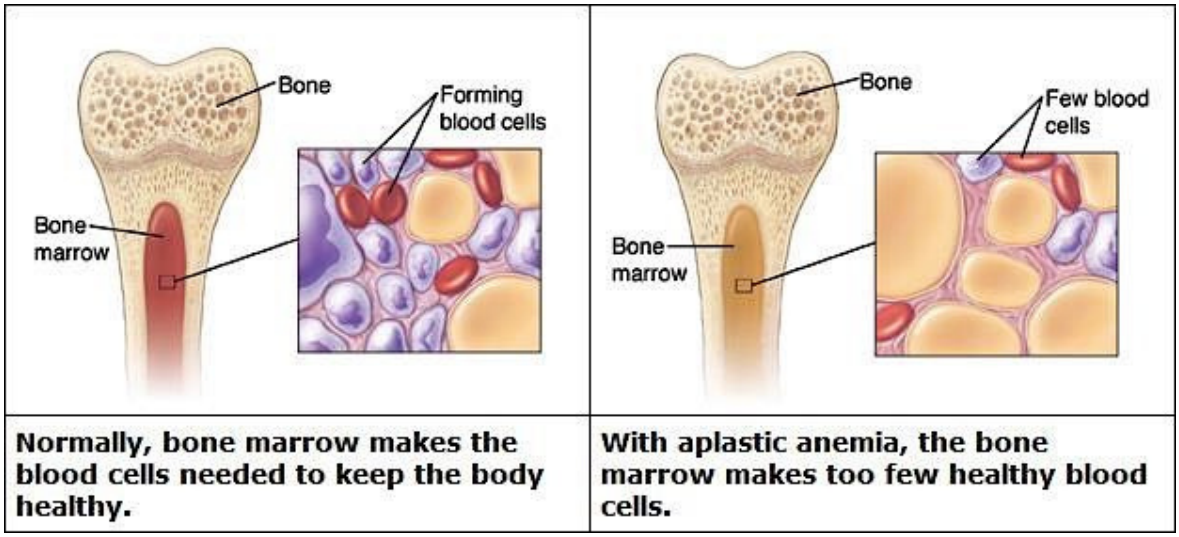


- **Lab Findings:**
  - **Cord Blood:**
    - Rh-D Antigen Present (Positive)
    - Positive Direct Coomb's Test (Ie: Mother's Anti-D Antibodies detected on Foetal RBCs)
    - ↑ Bilirubin
  - **Maternal Blood:**
    - Rh-D Antigen Absent (Negative)
    - Positive Indirect Coomb's Test (Ie: High levels 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 fetal Rh-Positive Blood cells (that cross the placenta) before the immune system has time to become sensitized

Mother's Rh factor	Father's Rh factor	Baby's Rh factor	Precautions
Rh positive	Rh positive	Rh positive	None
Rh negative	Rh negative	Rh negative	None
Rh positive	Rh negative	Could be Rh positive or Rh negative	None
Rh negative	Rh positive	Could be Rh positive or Rh negative	Rh immune globulin injections

APLASTIC ANAEMIA (Ie: MARROW FAILURE):

- (Aplastic Anaemia = "Pancytopenia with Bone Marrow *Hypo*cellularity (aplasia))
- **Aetiology:**
  - o **Simple Bone Marrow Failure (NOT Malignant)**
    - § **Primary:**
      - Congenital
      - Idiopathic
    - § **Secondary:**
      - Cytotoxic Drugs
      - Sensitivity to other drugs (Eg: Chloramphenicol, Chlorpromazine, Phenytoin, NSAIDs)
      - Ionizing Radiation
- **Pathogenesis:**
  - o Reduction in Pluripotent Stem Cells
  - o Remaining Stem Cells are *FAULTY* or *IMMUNOGENIC:*. Cannot repopulate the Marrow
  - o → Pancytopenia (Deficiency of all cells)
- **Morphology:**
  - o Pancytopenia with Bone Marrow *Hypo*cellularity (Aplasia)
  - o There are NO Leukemic, Cancerous or Abnormal Cells in Marrow OR Peripheral Blood
- **Clinical Features:**
  - o **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)
  - o **Investigations:**
    - § ****Bone Marrow Biopsy** – For Hypocellularity – Necessary for Diagnosis
    - § **Reticulocyte Count** – Complete *Absence* of Retics
    - § **Blood Count** – Pancytopenia
  - o **Treatment:**
    - § ***Bone Marrow Transplant + Supportive Transfusions**



Source: Unattributable

POLYCYTHAEMIA

POLYCYTHAEMIA/ERYTHROCYTOSIS (EXCESS RBCS):

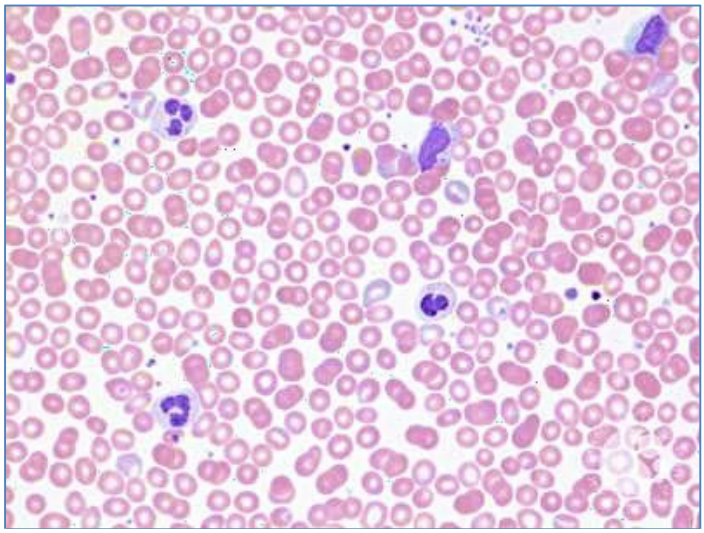
- **Aetiology:**
  - o **"True" Polycythaemia:**
    - § **Primary:**
    - § • *Polycythaemia Vera* (Primary Proliferative Polycythaemia)

      Secondary:
      - Tissue Hypoxia – Smoking (Co), High altitude, Pulmonary disease, Cyanotic Heart
      - Excess EPO – Renal Diseases (Hydronephrosis/Cysts/Carcinoma)
  - o **Relative "Spurious" Polycythaemia:**
    - § Dehydration - Dehydration
- **Pathogenesis:**
  - o **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)
  - o **Excess EPO:**
    - § Tissue Hypoxia → Renal Hypoxia → Stimulates EPO Secretion → ↑Erythropoiesis
  - o **Spurious Polycythaemia:**
    - § Dehydration → ↓Plasma Volume → Relative ↑ in RBC Concentration
- **Morphology:**
- o Hypercellular Marrow with Erythroid Hyperplasia

Clinical Features:

- o Most common in Elderly (>60yrs)
- o May be Asymptomatic
- o **Vague Symptoms of Hyperviscosity:**
  - § Headaches
  - § Dizziness
  - § Tinnitus
  - § Visual Disturbances
- o **Pathognomonic Symptoms:**
  - § Itch after a Hot Bath
  - § Burning sensation in fingers & toes (AKA: Erythromelalgia) – Relieved by cold
- o **Signs:** Facial Plethora
  - § Splenomegaly
  - § Signs of Art/Ven Thrombosis
  - §

- **Treatment:**
  - o **Treat Underlying Cause**
  - o **Venesection**
  - o **Anticoagulation/Antiplatelet**



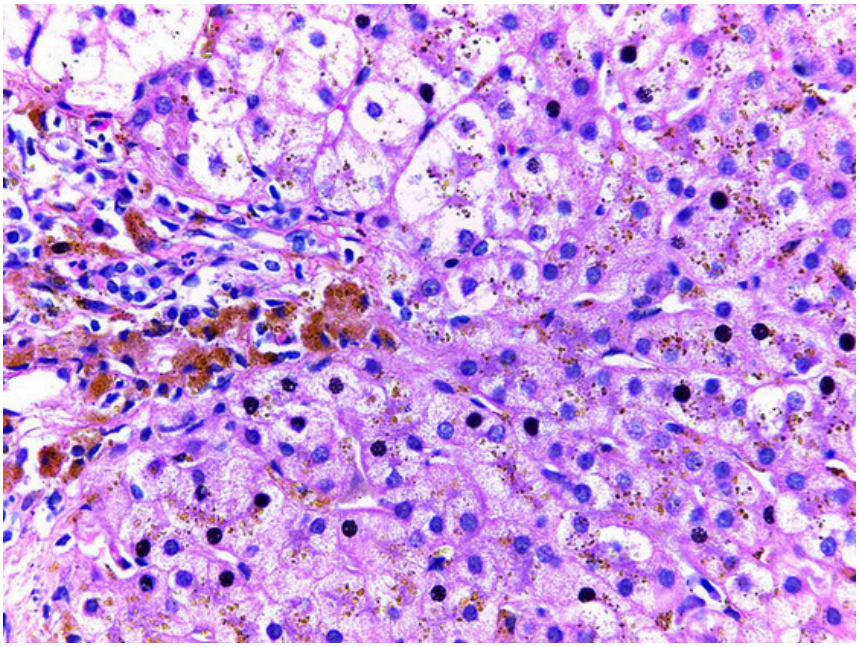
https://imagebank.hematology.org/reference-case/73/polycythemia-vera-with-progression

HAEMOCHROMATOSIS

HAEMOCHROMATOSIS:

- **Aetiology:**
  - **(Iron Overload in the Body Due to):**
    - **Primary – (**Hereditary 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**

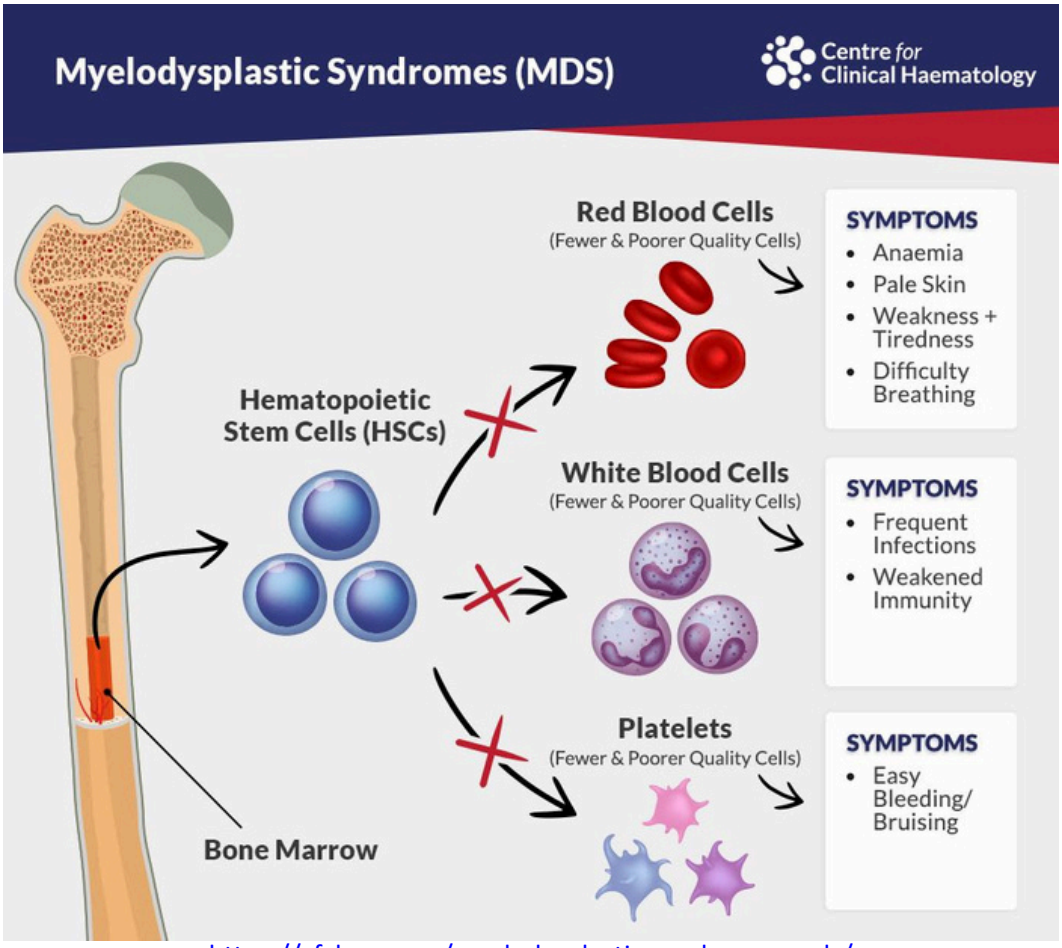
Haemochromatosis Liver with Coarse Hemosiderin Granules Within Hepatocytes



MYELODYSPLASTIC (PRELEUKAEMIC) SYNDROMES

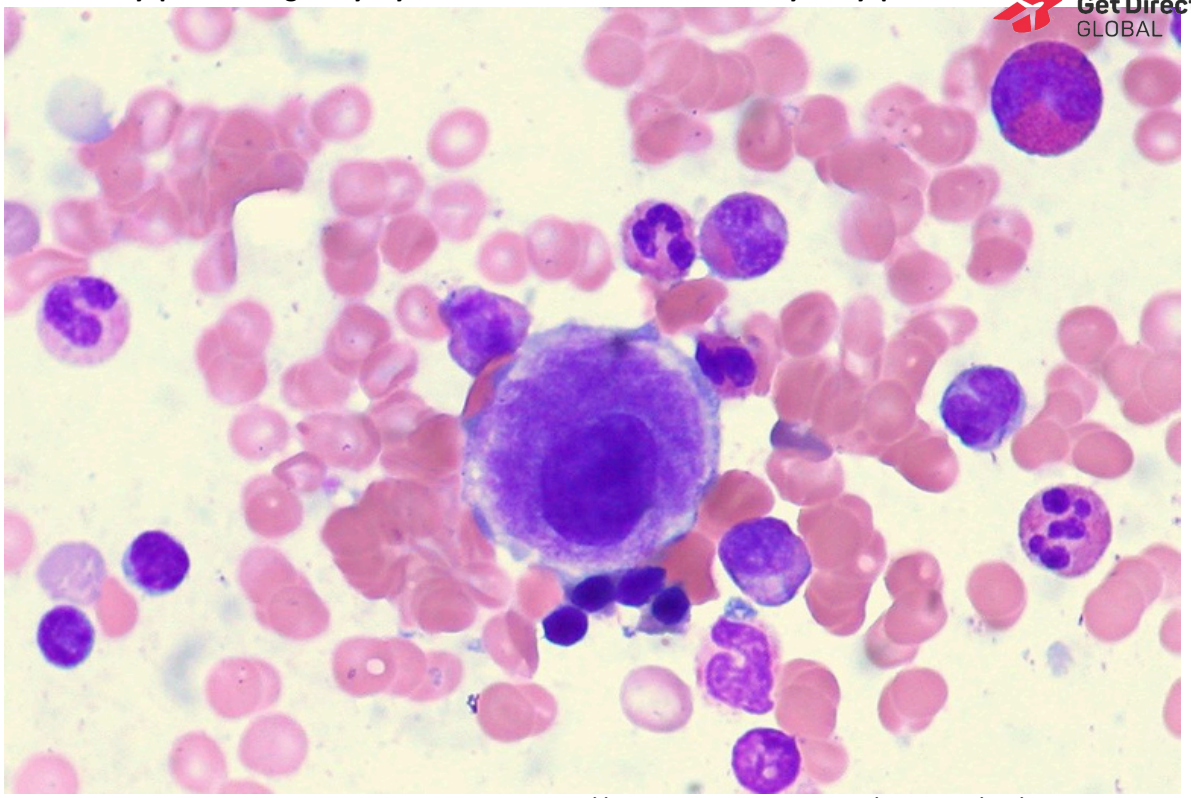
MYELODYSPLASTIC (*PRELEUKAEMIC*) SYNDROMES:

- **Pathology:**
  - **Defective Myeloblast (Myeloid Stem Cell) Differentiation → Marrow Failure → Pancytopenia →**
    - Anaemia
    - Thrombocytopenia → Bleeding
    - Neutropenia → Infection
  - ***Preleukaemic - 30% May Transform to Acute Leukaemias***
- **Morphology:**
  - **Bone Marrow –** Hypercellular (Despite Pancytopenia)
    - + 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
  - **→Often leads to Acute Myeloid Leukaemia**
- **Diagnostic Triad:**
  - **1-** One or More Cytopaenias (Anaemia +/- Thrombocytopenia +/- Neutropenia)
  - **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**



https://cfch.com.sg/myelodysplastic-syndromes-mds/

Dysplastic Megakaryocyte in Marrow of Patient with Myelodysplastic Disorder



MULTIPLE MYELOMA

MULTIPLE MYELOMA:

- **Aetiology:**
- o Malignancy (Overproduction) of *FUNCTIONING* **Plasma Cells** in Bone Marrow

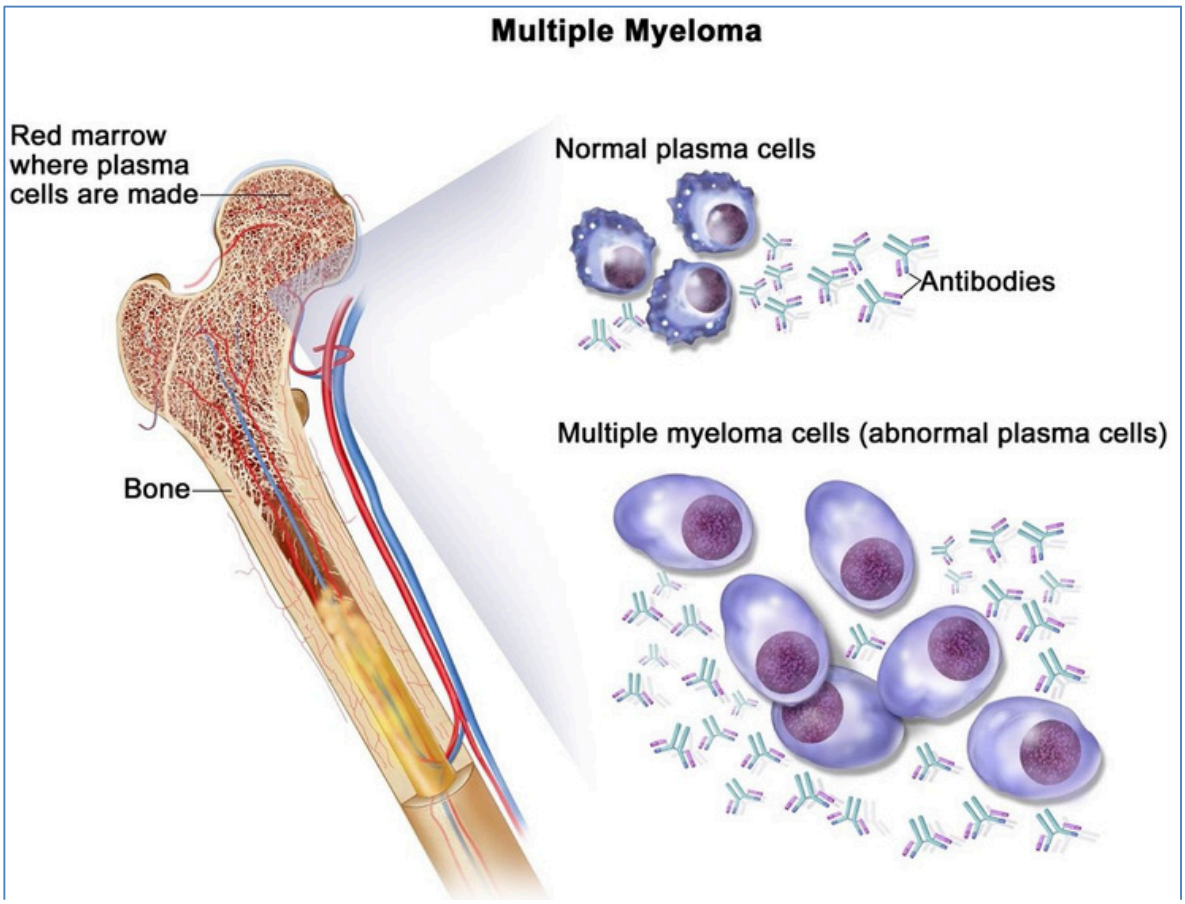
Pathology:

- o **Over-Proliferation of Plasma Cells** →
  - § → Only Produces ***Monoclonal*** Igs → **Recurrent Infections**
  - § + → Increased **Osteoclastic Activity** → **Lytic Bone Lesions** → Bone Pain

- **Clinical Features:**
  - o **Elderly, Males**
  - o **Symptoms:**
    - § **Bone Pain** (Typically Back Pain – Vertebral Involvement)
    - § **BM Failure -** Anaemia/Bleeding/Recurrent Infections
  - o **Signs:** **Pathological Fractures**
    - § **Hypercalcaemia**
    - § **BM Failure** → Aaemia/Bleeding/Infection
    - § **Ig Deposition in Renal Tubules** → Renal Impairment
    - § **Recurrent Infections**
    - §

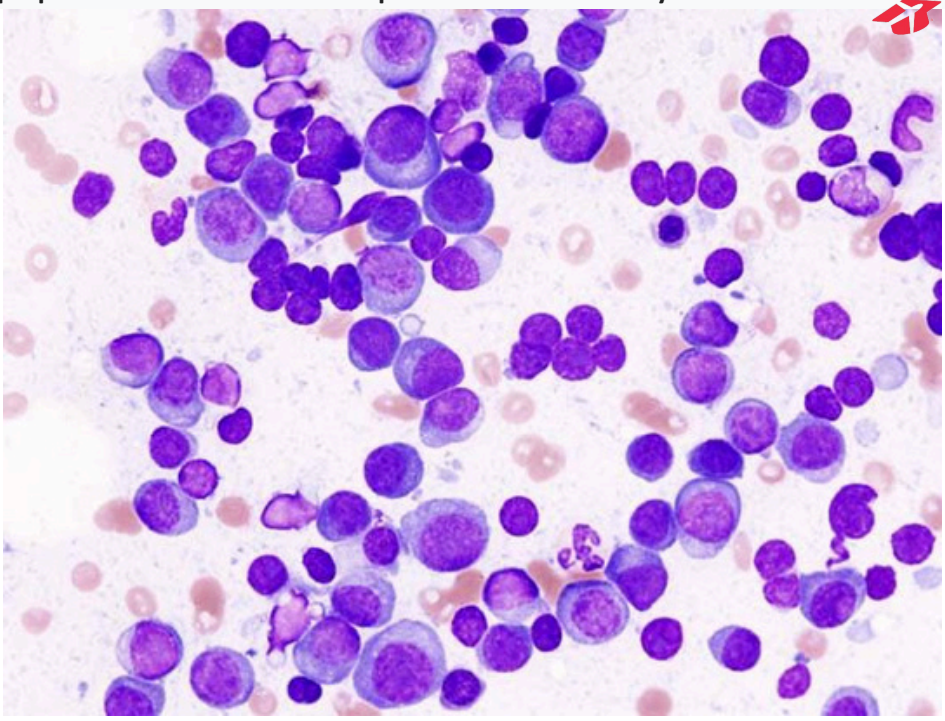
- **Diagnosis:**
  - o **FBC & Blood Film – (**↑↑Plasma Cells (BM & Peripheral Blood)**)**
  - o **↑ESR/CRP**
  - o **UEC – (**↑Ca**)**
  - o **CT/MRI/XR** – Lytic Bone Lesions
  - o **BM Biopsy** – Infiltration of BM by Plasma Cells

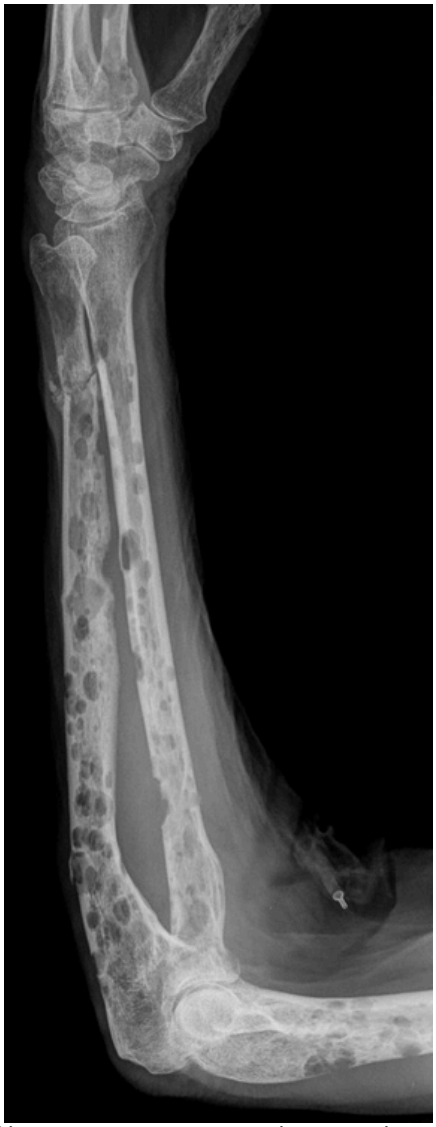
- **Treatment:**
  - o Supportive Treatment – Transfusions/Antibiotics
  - o **Allogeneic *BM Transplant***
  - o ***Bisphosphonates Inhibit Osteoclast Activity***
  - o ***Radiotherapy/Chemotherapy***



https://www.cancer.gov/types/myeloma/patient/myeloma-treatment-pdq

Smear preparation of bone marrow aspirate stained with May-Grünwald-Giemsa procedure





LEUKAEMIAS

LEUKAEMIAS

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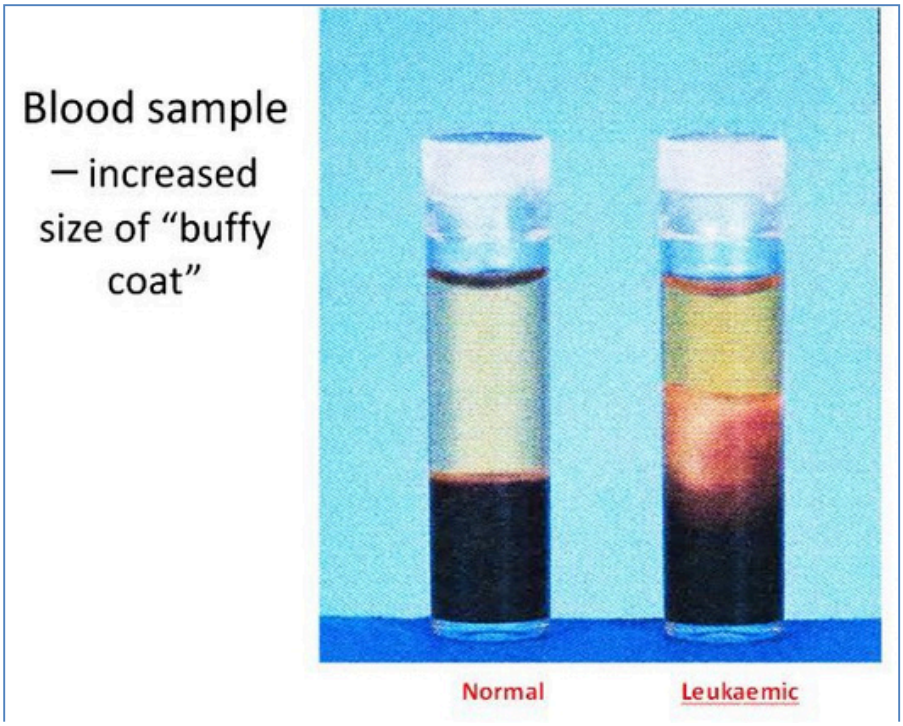
W hat Are Leukaem ias?:

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

- **Mutation** – Genetic Alteration within a *Single Myeloid OR Lymphoid Tissue* Progenitor
  - o **Chromosomal Translocations:**
    - § ***Philadelphia Chromosome:**
      - *#1 Cause of:* → *CHRONIC MYELOID LEUKAEMIA
  - o **Chromosomal Deletions/Additions:**
    - § ***Monosomy 7:**
      - *#1 Cause of:* → *ACUTE MYELOID LEUKAEMIA
  - o **Point Mutations**
  - o **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-Suppressive* Gene → Hyperactive Proliferation

Result:

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



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**

Classifications of Leukaemia:

- ***Acute* OR *Chronic:***
  - See table below
- ***Myeloid* OR *Lymphoid***
  - See table below

Other:

- **Hairy-Cell Leukaemia**
- **Prolymphocytic Leukaemia**
- **T-Cell Leukemic Lymphoma**

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

(Note: 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:

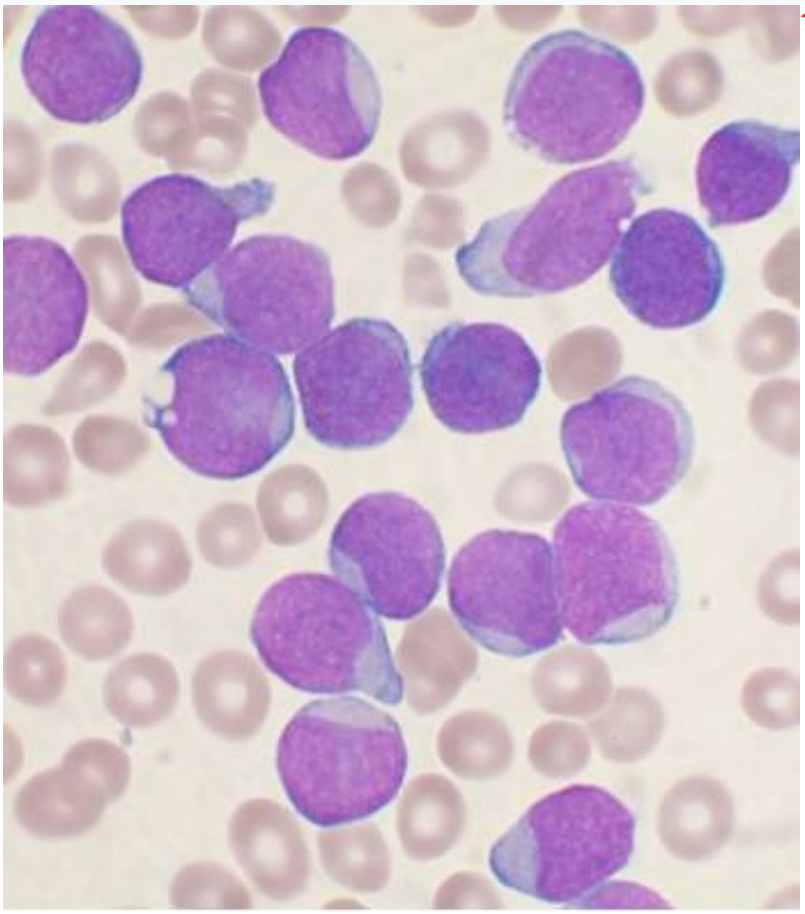
- **Aetiology:**
- o Genetic / Environmental

Pathogenesis:

- o Malignancy of ***Lymphoblasts*** → Uncontrolled Proliferation →
- o → Excess B-Lymphoblasts (B-Lymphocyte Precursors)
- o → Overcrowds the normal cells in the Bone Marrow
- o → Bone Marrow Failure
- o → Metastases (Bone, Liver, Spleen, Lymph Nodes)
- o → → Can be fatal in weeks to months if left untreated

- **Clinical Features:**
  - o **Most Common in Young Children (4-5yrs)**
  - o **Good Prognosis (70-90% Cure Rate) (Low Mortality)**
  - o **Signs & Symptoms:**
    - § **Bone/Joint Pain** (Especially sternum)
    - § **Marrow Failure →**
      - **↓Hb → Anemia** → Pallor, weakness, fatigue, dyspnea
      - **↓Platelets → Thrombocytopenia** → Bruising & bleeding
      - **↓WCC → Neutropenia** → Frequent Fevers & Infections
    - § **Organomegaly (**Liver, Spleen**)**
    - § **Lymphadenopathy** (Incl: Mediastinal)
    - § **Weight-Loss/Loss of Appetite**
    - § **Oedema in Lower Limbs**
- **Diagnosis:**
  - o **Physical Examination**
  - o **Complete Blood Count:**
    - § Excess Abnormal Leukocytes (↑WCC)
    - § Blast Cells (Big, Immature Cells)
    - § Anaemia (↓Hb)
    - § Thrombocytopenia (↓PLTs)
  - o **Blood Film** - Characteristic ***Lymphoblast*** Cells
  - o **Bone Marrow Biopsy**
    - § Required for *Definitive* Diagnosis
    - § Characteristic ***Lymphoblast*** Cells
  - o **Cytogenetics:**
    - § Testing for Chromosomal Translocations
    - § Particularly for the 'Philadelphia Chromosome'
  - o **Cytochemistry:**
    - § Using *Cytochemical Stains* to Differentiate between AML & ALL
    - § Stains = Myeloperoxidase & Sudan Black Stain
      - AML – Positive with Both Stains
      - ALL – Negative with Both Stains
  - o **CXR/CT** – Mediastinal/Abdominal Lymphadenopathy
- **Treatment:**
  - o o **Supportive –** Transfusions/Fluids
  - o **Chemotherapy –** Aim for Remission &
  - **IV Antibiotics –** + Antivirals/Antifungals
  - **Allogeneic Marrow Transplant**

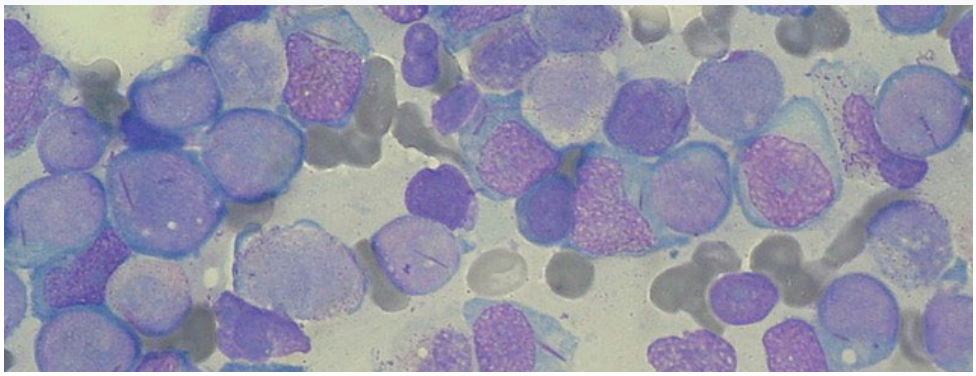
A Wright's stained bone marrow aspirate smear of patient with precursor B-cell acute lymphoblastic leukemia



AML - ACUTE MYELOID LEUKAEMIA:

- **Aetiology:**
  - o Genetic / Environmental
  - o Or Progression from Myelodysplastic States
- **Pathology:**
  - o Malignancy of ***Myeloblasts*** →Uncontrolled Proliferation →
  - o → Accumulation in the Bone Marrow →
  - o → 'Packs Out' the bone→ interfere with the production of normal blood cells
  - o → Bone Marrow Failure
  - o → Metastases
- **Clinical Features:**
  - o **Poor Prognosis (High Mortality)**
  - o **Most Common in ADULTS** –↑Incidence with Age
- **Signs & Symptoms:**
  - o **Bone Pain** (Especially sternum)
  - o **Marrow Failure →**
    - § **↓Hb → Anemia** → Pallor, weakness, fatigue, dyspnea
    - § **↓Platelets → Thrombocytopenia** → Easy Bruising & bleeding
    - § **↓WCC → Neutropenia** → Vulnerable to Infections
  - o **Organomegaly (**Liver, Spleen**)**
  - o **Lymphadenopathy** (Incl: Mediastinal)
    - § **Gum Hypertrophy**
- **Diagnosis:**
  - o **Complete Blood Count:**
    - § Excess Abnormal Leukocytes (↑WCC)
    - § Blast Cells (Big, Immature Cells)
    - § Anaemia (↓Hb)
    - § Thrombocytopenia (↓Plts)
  - o **Blood Film** - Characteristic ***Myeloblast*** Cells
  - o **Bone Marrow Biopsy** - Characteristic ***Myeloblast*** Cells with pathognomonic **"Auer Rods"**
  - o **CXR/CT** – Mediastinal/Abdominal Compression & Infection
  - o **Cytogenetics:**
    - § Testing for Chromosomal Translocations
  - o **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:**
  - o **Supportive –** Transfusions/Fluids
  - o **IV Antibiotics -** + Antivirals/Antifungals
  - o **Chemotherapy –** Aim for Remission
  - o **Allogeneic Marrow (Haematopoietic Stem Cell) Transplant**

Myeloblasts with Auer rods seen in Acute Myeloid Leukemia (AML), advanced stage. Bone Marrow



CLL - CHRONIC LYMPHOCYTIC LEUKAEMIA:

- **Aetiology:**
- o Thought to be acquired Genetic Mutations over time → Malignancy

Pathology:

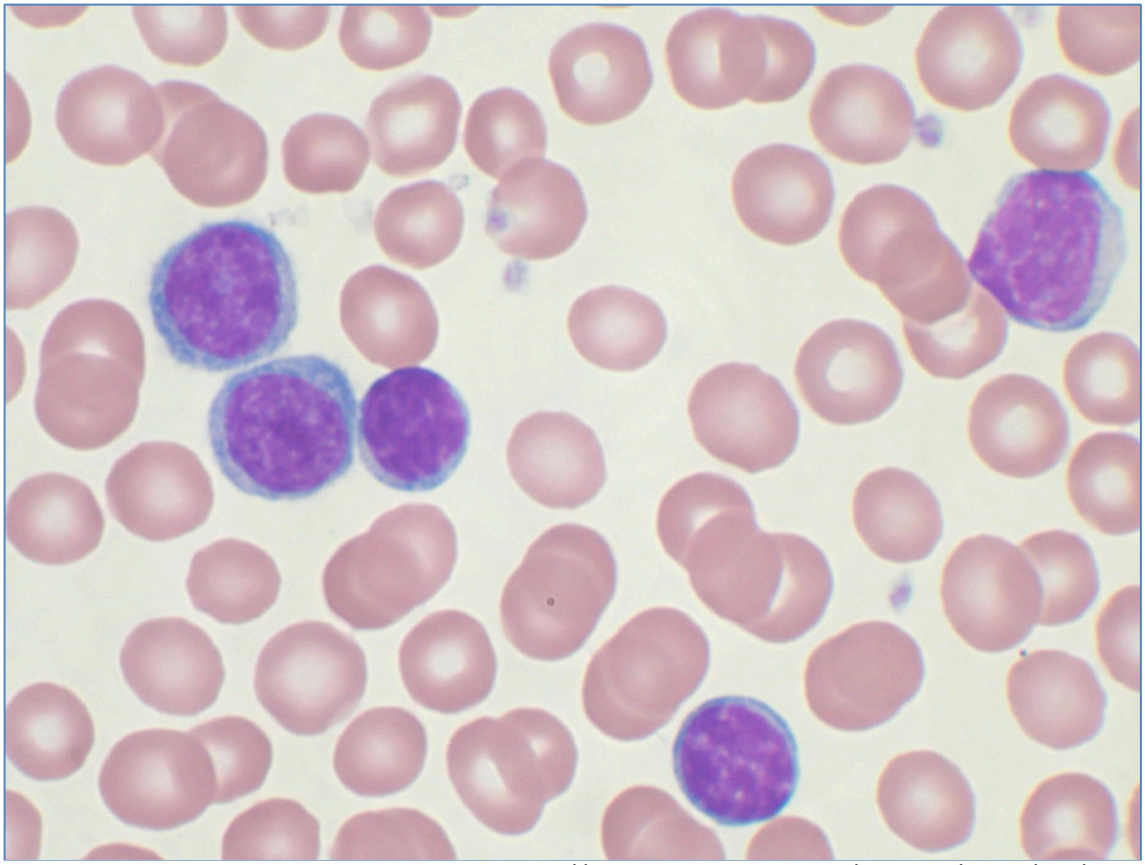
- o Malignancy of ***Neoplastic, Mature, Poorly-Functioning B-Cells*** →
- o → Overproliferation of Mutated B-Cells → Can't Fight Infection
- o → The cells accumulate mainly in the bone marrow and blood
- o Slow Bone Marrow Failure→ & Slow Metastasis

- **Clinical Features:**
  - o ***The Commonest Leukaemia, Mainly in Elderly (50-60yrs)***
  - o ***Good Survival – 9yr Median Survival – But NO CURE*** (Death due to infection, not mets)
  - o **Symptoms:**
    - § **Typically Asymptomatic @ Dx – 60%** **(Diagnosed on routine blood test)**
    - § **If Bone Marrow Failure** – (Anaemia, Recurrent Infection, Bruising)
    - § **If Severe** – Weight Loss, Sweats, Anorexia
  - o **Signs:** Lymphadenopathy (Especially Cervical) Enlarged, Rubbery, *Non-Tender*
    - § Organomegaly (Especially Splenomegaly, Hepatomegaly)
    - §
- **Diagnosis:**
- o **Blood Count & Film – (**↑↑Lymphocytosis, Anaemia, Neutropenia, Thrombocytopenia**)**

Treatment:

- o **Early CLL is not treated**
- o ***CLL is only Treated when symptoms affect Quality of Life***
- o **Late CLL treated with:**
  - § **IV-Ig** – For Infections;
  - § **Chemotherapy/Radiotherapy** – Palliative
- o **(Stem Cell Transplant – Curative)**

Wright's stained peripheral blood smear showing chronic lymphocytic leukemia (CLL). The lymphocytes with the darkly staining nuclei and scant cytoplasm are the CLL cells.



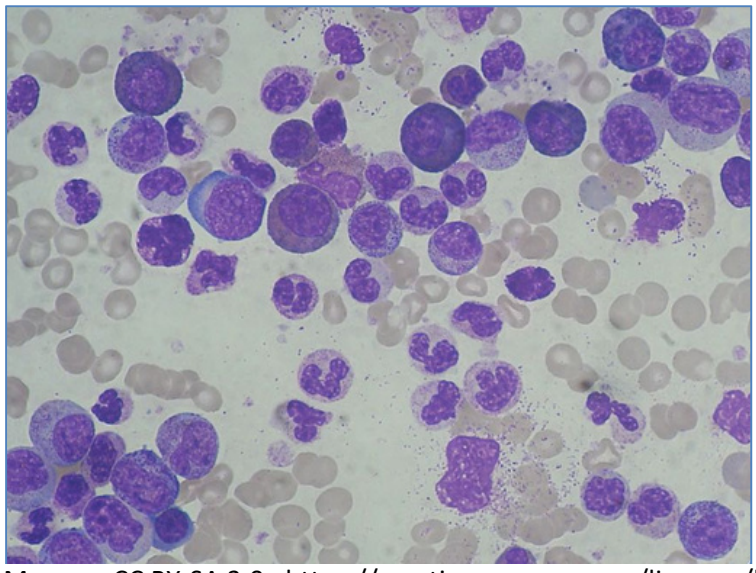
CML - CHRONIC MYELOID LEUKAEMIA:

- **Aetiology:**
- o **Genetic (Philadelphia Chromosome - >80%)**

Pathogenesis:

- o **Myeloid Proliferation in Bone Marrow & Blood →**
  - § → High, unregulated growth of myeloid cells
  - § → Accumulation of immature granulocytes (neutrophils/eosinophils/basophils)
- o ***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):
    - 'Blast Crisis' is imminent
    - Fatal Acute Leukemic Phase
    - Final phase in the evolution of CML
    - Behaves like an acute leukaemia
    - Rapid Progression + Short survival
    - Requires Immediate Bone Marrow Transplant to Survive

- **Clinical Features:**
  - o **Middle-Age (40-60yrs)**
  - o **Symptoms:**
    - § **Often Asymptomatic** (Usually detected by routine blood tests)
    - § **BM Failure:**
      - **Anaemia – Low [Hb] (due to ↓RBCs)**
      - **Thrombocytopenia – (Low Platelets)**
      - **Neutropenia – (Infection)**
    - § **Malaise** (general feeling of being unwell)
    - § **Fever, Weight Loss, Fatigue**
    - § **Abdo Discomfort** (**Splenomegaly**)
    - § **Gout** (Metabolic Arthritis – Due to ↑[Uric Acid] in blood)
  - o **Signs:**
    - § **Organomegaly** in >75%
    - § Anaemia/Bruising
    - §
- **Diagnosis:**
  - o **FBC/Blood Smear** - ↑↑WCC with ↑All Myeloid Cell Types
  - o **Marrow Biopsy** - Hypercellular Marrow
  - o **Molecular Genetics** - Philadelphia Chromosome
- **Treatment:**
  - o **Chronic Phase: Chemotherapy** – ***Glivec (Imatinib)*** – **A Tyrosine Kinase Inhibitor**
  - o ****Blast Crisis*****:** Requires Immediate Bone Marrow Transplant to Survive



LYMPHOMAS

LYMPHOMAS:

Get Direction GLOBAL

HODGKIN'S LYMPHOMA (15%):

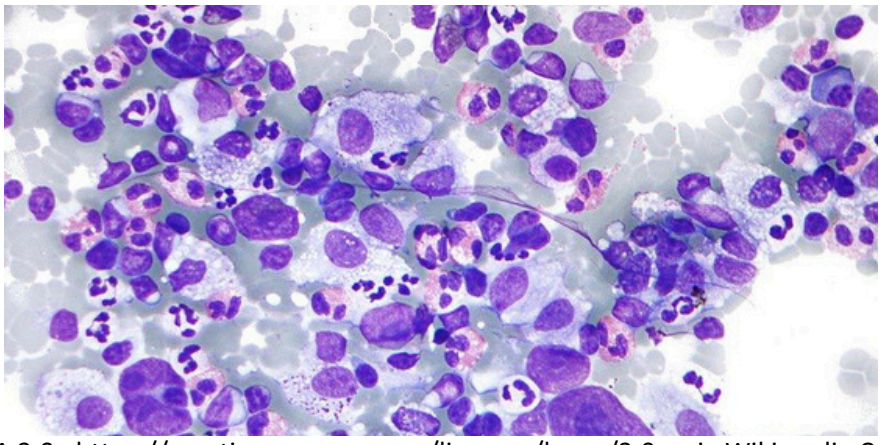
- **Aetiology:**
  - **Idiopathic**
  - **Risk Factor = EBV (Infective Mononucleosis)**
- **Pathology:**
- **Malignant Lymphocytes** → Accumulate in Lymph Nodes, Peripheral Blood & Other Organs

Clinical Features:

- **Bimodal Age Distribution**
  - Young Adulthood (15-35)
  - Late Adulthood (55+)
- **Good Prognosis** – High Cure Rate
- **Signs & Symptoms:**
  - ***Asymmetrical & Painless Lymphadenopathy** – Non-Tender, Rubbery (Neck, Axillary)
  - **Systemic "B" Symptoms –** (Fever, Night Sweats, Weight Loss, Fatigue)
  - **Splenomegaly/Hepatomegaly**
  - **Pathognomonic Symptoms:**
    - Pruritis
    - Alcohol Induced Lymph Node Pain

- **Diagnosis:**
  - ***Lymph Node Biopsy -** Presence of ***Reed-Sternberg Cells***
  - ***Bone Marrow 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

Mixture of cells common in Hodgkin Lymphoma (Eosinophils, Reed-Sternberg cells, Plasma Cells)



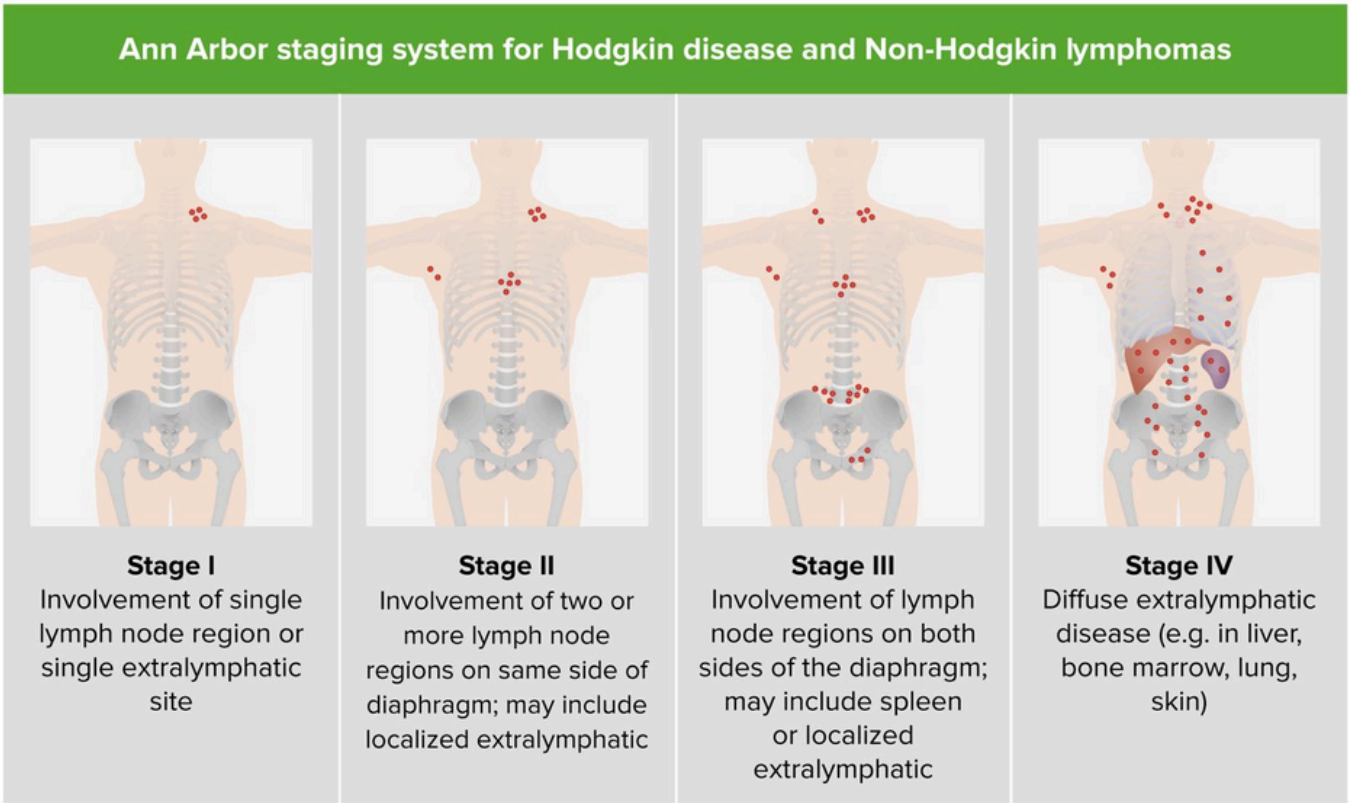
NON-HODGKIN'S LYMPHOMAS (85%):

- **What Are They?:**
  - o Diverse group of Haematologic Cancers, Encompassing Any Lymphoma *other than* Hodgkin's Lymphoma
  - o Complicated Classification
  - o Occur At Any Age
  - o May be Aggressive/Benign
- **Aetiology:**
  - o **Post-Viral Infections** – ***HTLV-1, EBV, HHV8, HIV, H-pylori***
  - o **Environmental Toxins** – ***Pesticides, Organic Solvents***
- **Pathology:**
- o **Malignant Lymphocytes** → Accumulate in Lymph Nodes, Peripheral Blood & Other Organs

Clinical Features:

- o ***POOR Prognosis – 5yrs for treated pts**
- o **Signs & Symptoms:**
  - § **Initially 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:**
  - o **Bone Marrow Biopsy** o **Lymph Node Biopsy**
  - o **CXR/CT** – for Staging
- **Treatment:**
  - o (Depends on Staging)
  - o **Radiotherapy may be Curative if Localised Disease**
  - o **Chemotherapy in Diffuse Disease**



Source: https://www.lecturio.com/magazine/non-hodgkins-lymphoma/

BLEEDING DISORDERS

BLEEDING DISORDERS

There Are Many Potential Causes Of Bleeding Disorders. Eg:

- **Vascular Disorders:**
  - o Abnormalities in Blood Vessel Structure or Perivascular Connective Tissue
  - o Leads to: Easy Bruising
- **Thrombocytopenia:**
  - o Due to ***deficient number of platelets***
  - o Results from either:
    - § ↓ Platelet Production
    - § ↑ Platelet Destruction
    - § ↑ Platelet Consumption (in large injuries/burns)
- **Defective Platelet Function:**
  - o There are enough platelets, but not working properly
  - o May be Inherited (rare)...OR
  - o Acquired: (Eg: From Aspirin/other blood thinners)
- **Von Willebrand's Deficiency:**
  - o Either Not enough vWF....or Dysfunction of vWF
  - o vWF is necessary for platelet adhesion. Therefore Deficiency → Poor platelet plug formation
- **Coagulopathy = Defective Coagulation:**
  - o **Bleeding disorders due to deficiency in 1 or more Coagulation Factors**
  - o **Hereditary Coagulopathies:**
    - § **Haemophilia A: Factor VIII Deficiency:**
      - Most common
      - Sex Linked Recessive (Female Carriers; Affected Males)
      - **Treatment - Recombinant** clotting factors
    - § **Haemophilia B: Factor IX Deficiency:**
      - AKA: Christmas Disease
      - Less common
      - Sex Linked Recessive (only affects males)
      - **Treatment - Recombinant** clotting factors
    - § **Other deficiencies (Factors V, VII, X, XI & XIII) Rare**
      - Just know they exist
  - o **Acquired Coagulopathies:**
    - § **Vitamin K Deficiency (Factors II, VII, IX, X)**
      - Dietary
      - Malabsorption
      - Or Long-term warfarin
    - § **Chronic Liver Disease:**
      - Eg: Biliary Obstruction:
        - o Hinders absorption of Fat-Soluble vitamins
        - o Reduced synthesis of Factors II, VII, IX & X
      - Eg: Severe Hepatocellular Damage:
        - o 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

Evaluation of Bleeding Disorders:

- **Platelet Count**
  - o Literally the number of platelets/volume of blood
  - o Normal range = 150-400x109/L
  - o Excessively Low platelet count → Thrombocytopenia (bleeding disorder)

- **Platelet Function Tests**
  - o **Complete Blood Count (CBC)/Full Blood Evaluation (FBE):**
    - § Include platelet count & morphology - Eg: Giant platelets
  - o **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
  - o **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:**
  - o **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
  - o **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
  - o **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

THROMBOTIC DISORDERS

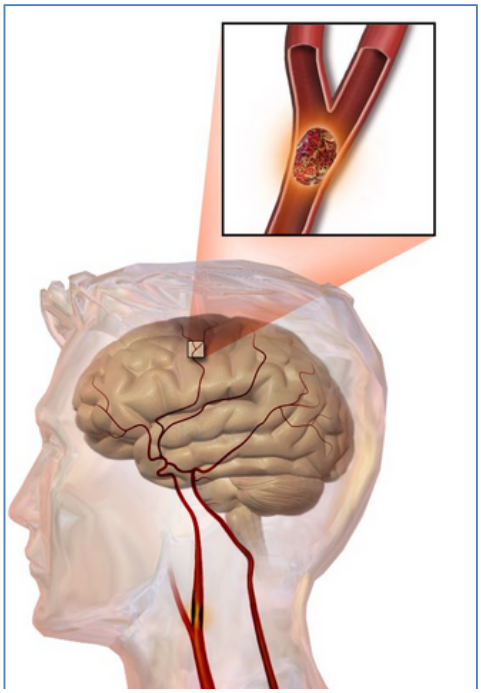
THROMBOTIC DISORDERS

Thrombosis = inappropriate formation of Platelet & Fibrin Clots

- Can cause obstruction to flow → Ischaemia → Necrosis
- **Can Move Elsewhere = "*ThromboEmbolism":***
  - o Most are asymptomatic
  - o Fragments move swiftly in large vessels
  - o 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:

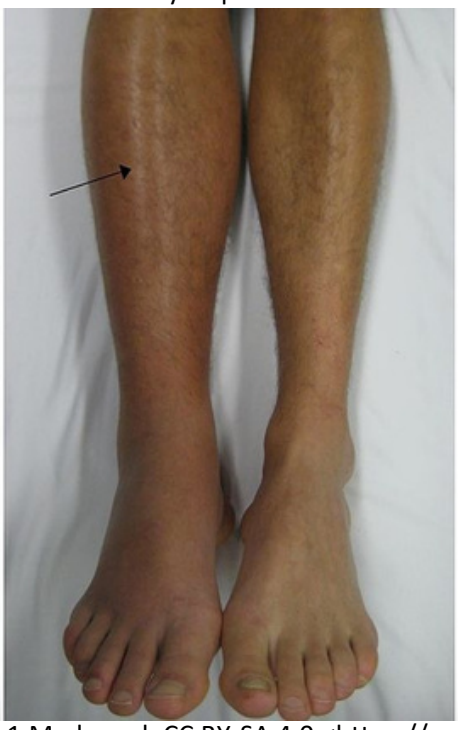
- **2 Mechanisms:**
  - o **1- Atherosclerotic Plaque Rupture in Arterial walls → Arterial Thrombosis**
    - § Ie: Rupture of Atherosclerotic Plaque →
      - Exposure of SubEndothelial Collagen
      - Exposure of Tissue Factor
      - → Thrombosis
  - o **2- Thromboembolism → Arterial Thrombosis**
    - § Eg: Atrial thrombus formation during Atrial Fibrillation → Embolus → CVA/Stroke
- **Risk Factors:**
  - o Family Hx
  - o Males (more common)
  - o ↑Cholesterol
  - o Diabetes
  - o ↑BP
  - o Smoking
  - o Obesity
  - o Age
- **Most common cause of:**
  - o **CerebroVascular Accidents (CVA's)** – aka: Stroke – Clot in brain → Necrosis of Neurons
  - o **Myocardial Infarction (MI)** – Due to Thrombi related to atherosclerosis in Coronary Arteries → Necrosis of Myocardium
  - o **Peripheral Arterial Disease (PAD)**

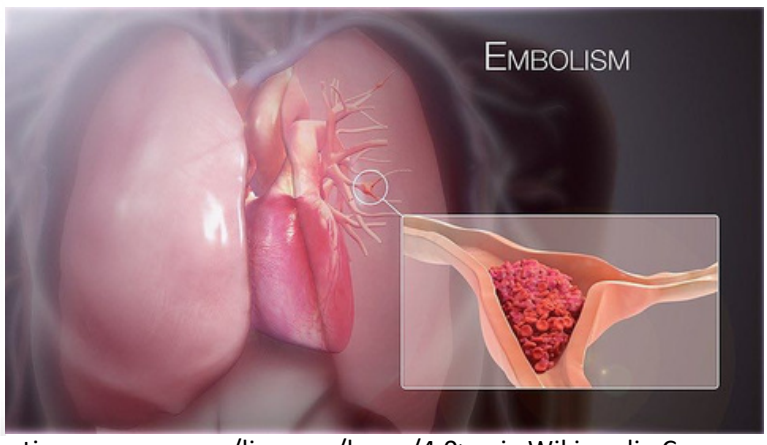


Venous Thrombosis:

- **Occur Mostly in Lower Extremities (due to gravity pooling blood)**
  - Includes Deep & Superficial Leg Veins
  - Patient may present with sore or swollen legs/calves
- **Risk Factors:**
  - **Hereditary Hypercoagulable States**:
    - Factor V mutation
    - Prothrombin variant
    - Protein C deficiency
    - Protein S deficiency
    - Antithrombin Deficiency
  - **Acquired Hypercoagulable States:**
    - **High-Dose Oestrogen Therapy:**
      - ↑Plasma levels of Coagulation 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 Coagulation Factors during pregnancy)**
    - **Sepsis (bacterial infection → widespread damage to endothelium)**
    - **Heparin-Induced Thrombocytopenia** (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 Coagulation Factors through Urine)
      - Varicose Veins
- **Treatment:**
  - Anticoagulation (Either oral or parenteral)
  - Treat any Haemodynamic Instability of underlying cause
  - Clot may require endovascular retrieval





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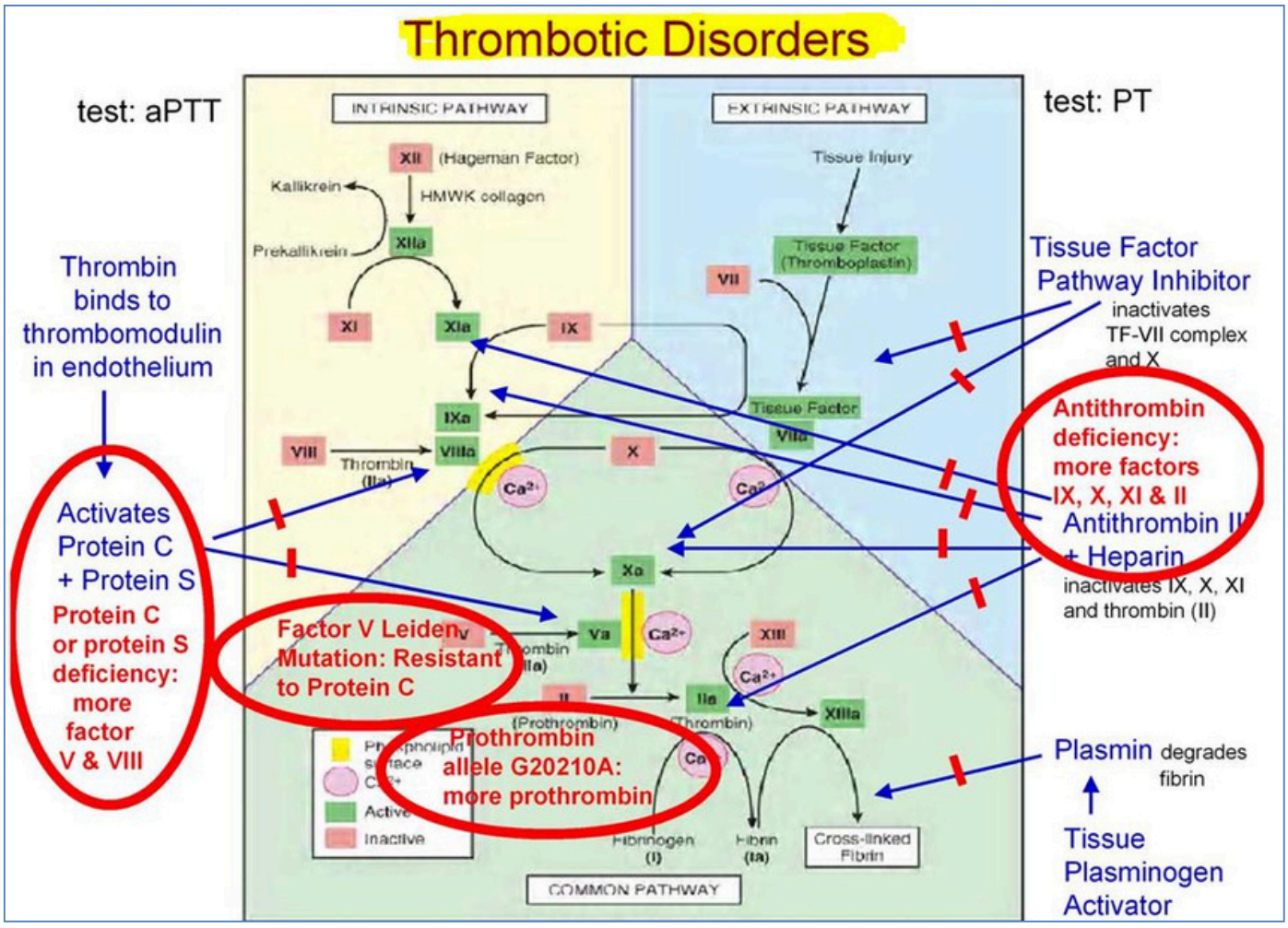
Evaluation of Thrombotic Disorders:

- **Required if:**
  - o Family History of Thrombosis
  - o Thrombosis at young age/unusual site
  - o Recurrent DVT
- **Complete Blood Count ...&...Erythrocyte Sedimentation Rate:**...Detect:
  - o Change in Haematocrit
  - o Change in White Cell Count
  - o o Change in Platelet Count
  - o Red cell fragmentation Change in Fibrinogen
- **Prothrombin Time (PT):**
  - o *Time taken for plasma to clot after addition of tissue factor (Factor III)*
  - o See above section for details
  - o *Detects deficiency of Factor VII*
- **Activated Partial Thromboplastin Time (aPTT):**
  - o *Time taken for plasma to clot after addition of phospholipids*
  - o See above section for details
  - o *Detects deficiency of Factors VIII, IX, XI or XII*
- **If *Both* PT & aPTT are Abnormal:**
  - o *Probably due to:*
    - § *Liver disease*
    - § *Vit-K Deficiency……..or*
    - § *Oral Anticoagulants*
- **INR –** If on Warfarin (Dose too low)



DRUGS FOR HAEMOSTASIS

DRUGS FOR HAEMOSTASIS

Get Direction GLOBAL

Factors Involved in Haemostasis – (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:

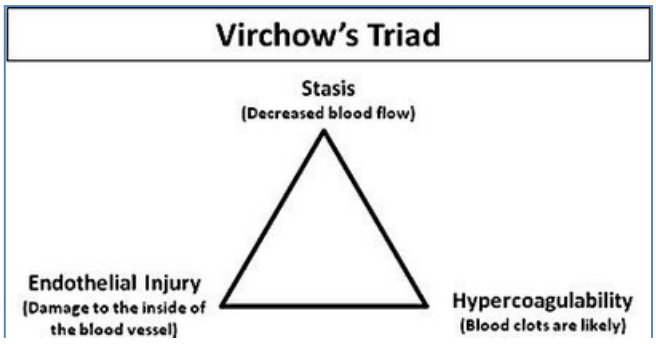
- Tissue **Plasminogen Activator** → Activates Plasminogen to become Plasmin
- (Plasmin degrades fibrin clots)

Remember, 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

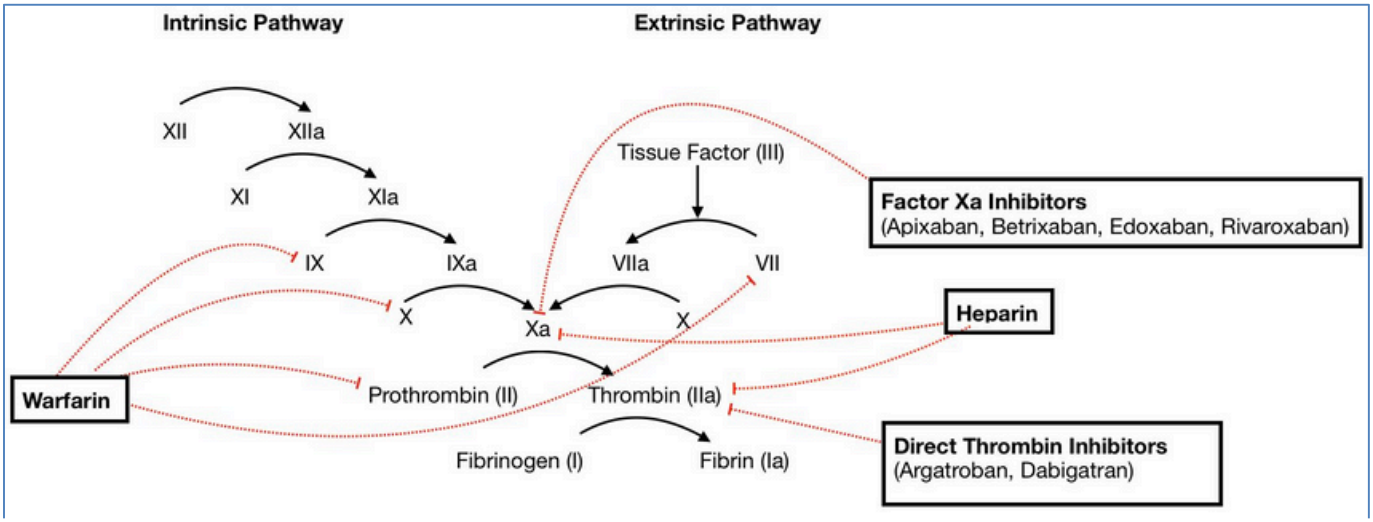
Virchow's Triad: – Formation of Thrombosis:

- **Three Conditions Predispose to Inappropriate Thrombus Formation:**
  - **1- Endothelial Injury:**
    - Eg: Atherosclerosis
    - Eg: Aneurysm
    - Eg: Blood Vessel Disorders (Eg: Hereditary Haemorrhagic Telangiectasia)
  - **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)



ANTI-COAGULANTS:

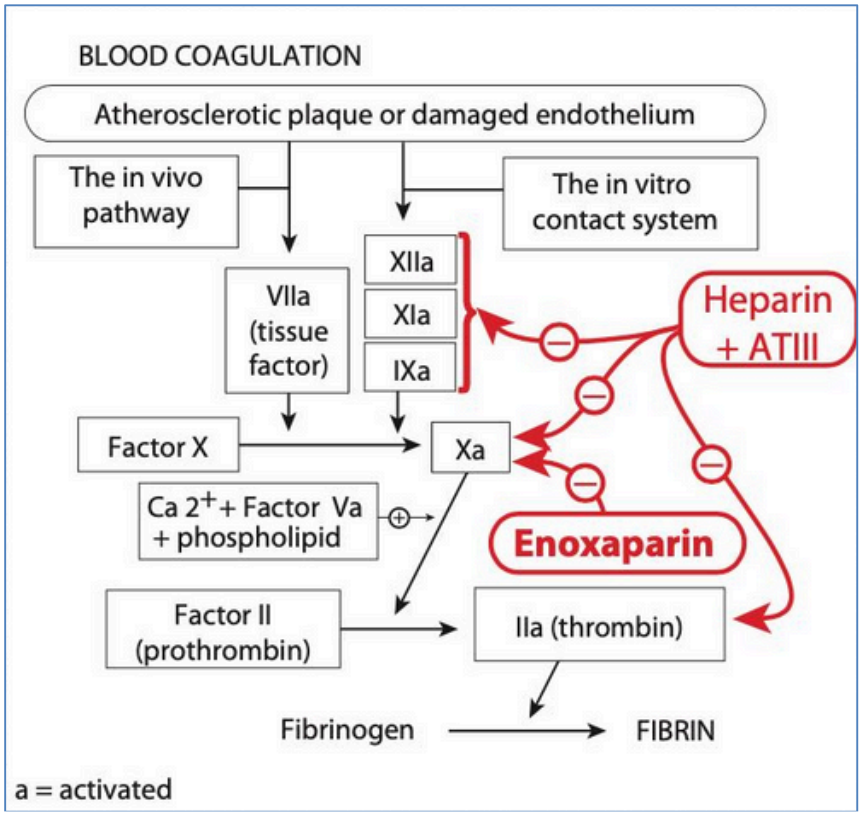
- **Heparin (Including Low Molecular-Weight Heparins):**
  - **Mechanism of Action:**
    - § Binds & Activates ***Antithrombin-III*** to form an ***AT-III:Heparin Complex***
    - § The ***AT-III:Heparin Complex*** →:
      - 1- → **Inactivates Thrombin (Factor-II):**
      - o Therefore Inhibits activation of Prothrombin to Thrombin
      - 2- → **Inactivates Factor-X:**
      - o 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)
    - § *Thrombocytopenia – (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

- ***Thrombocytopenia – *As a Side-Effect of Heparin*:**
  - **What is Thrombocytopenia?**
    - § Thrombocytopenia = Low number of Platelets
  - **What is *Heparin-Induced* Thrombocytopenia?**
    - § **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 Thrombocytopenia*:**
    - § *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 (→Thrombocytopenia)

- **Low Molecular-Weight Heparins (LMWH) – Eg: ENOXAPARIN:**
  - **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:**
        - o Therefore Inhibits activation of Fibrinogen to Fibrin
    - § **Note: *However,* LMWHs are *Too Small* to inactivate Thrombin :. Only target Factor-X**
  - **Advantages over *Normal* Heparin:**
    - § Longer T1/2
    - § 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)



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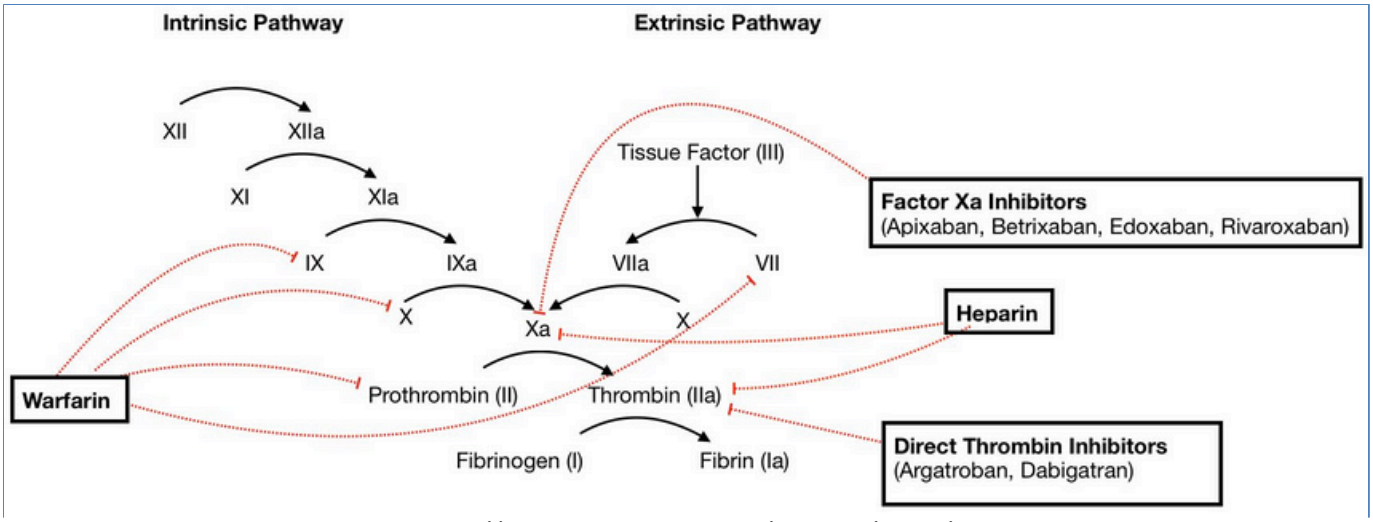
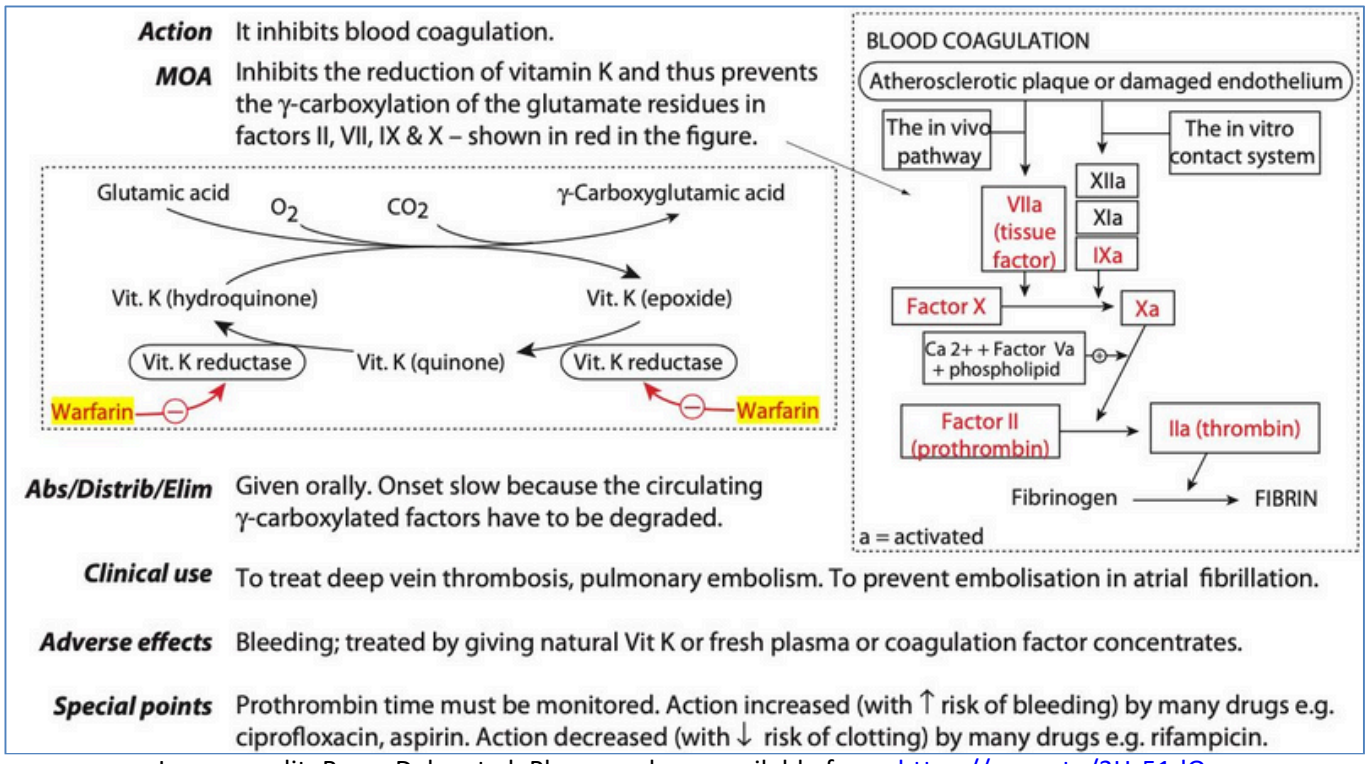
- **Coumarins/Coumadins (Warfarin):**
  - **Mechanism of Action:**
    - A **Vitamin-K Analogue** → Inhibits synthesis of Pro-Coagulation Factors:
      - ↓***Prothrombin***
      - ↓***Factor-II*** **(Thrombin)**
      - ↓***Factor-VII***
      - ↓***Factor-IX***
      - ↓***Factor-X***
    - **Explanation:**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





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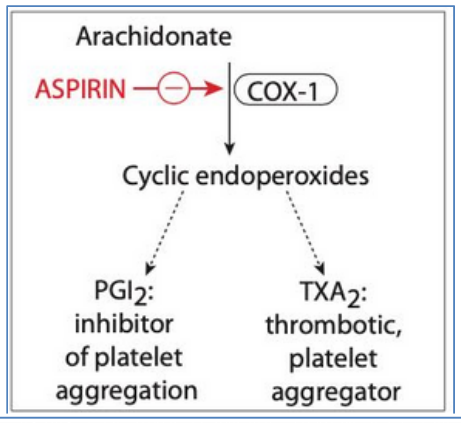
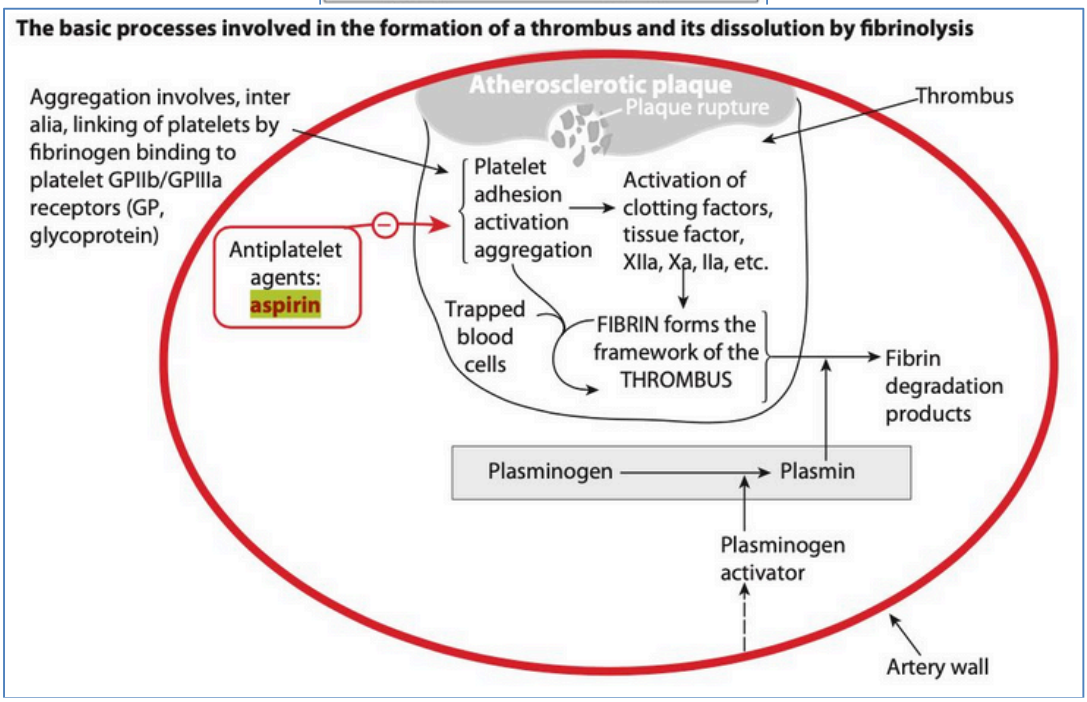
- **Side Effects:**
  - *Bleeding – (However ***Vitamin-K*** is an antidote)
  - Note: Many factors influence effectiveness:
    - (Diet/Alcohol/Body Mass/Other Meds/Alternative Meds/Comorbidity/genetics)
  - Is TERATOGENIC – *CONTRAindicated* in Pregnancy
- **Drug Interactions:**
  - Warfarin is metabolised 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

    Note: Vitamin-K can be used as an *Antidote* for Warfarin Overdose
    - Similarly, a high Vit-K diet can decrease warfarin's 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)
      - (Note: Thromboxane is a Platelet-Aggregator – Acts by stimulating the expression of the Glycoprotein receptor "GP-IIb/IIIa" → Aggregation)
    - **Note:** 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





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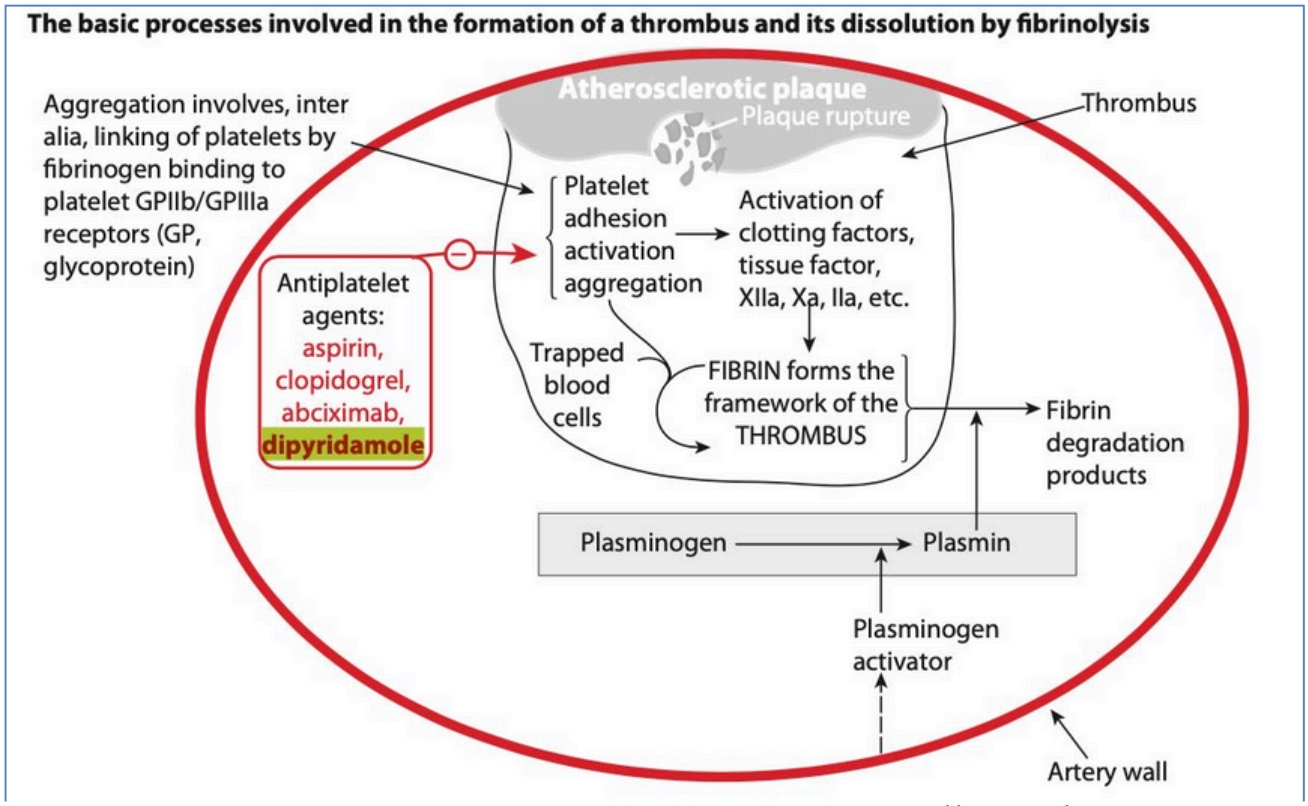
- **Indications:**
  - Reduce risk of Myocardial Infarction/Angina
  - Acute Stroke
- **Side Effects:**
  - GI-Bleeding (due to loss of Prostaglandins [which are protective by ↓Acid & ↑Mucus])
  - Toxic dose can cause Respiratory Alkalosis
- **Other Info:**
  - Note: Antiplatelet effects of Aspirin occur 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:**
      - (Note: 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)



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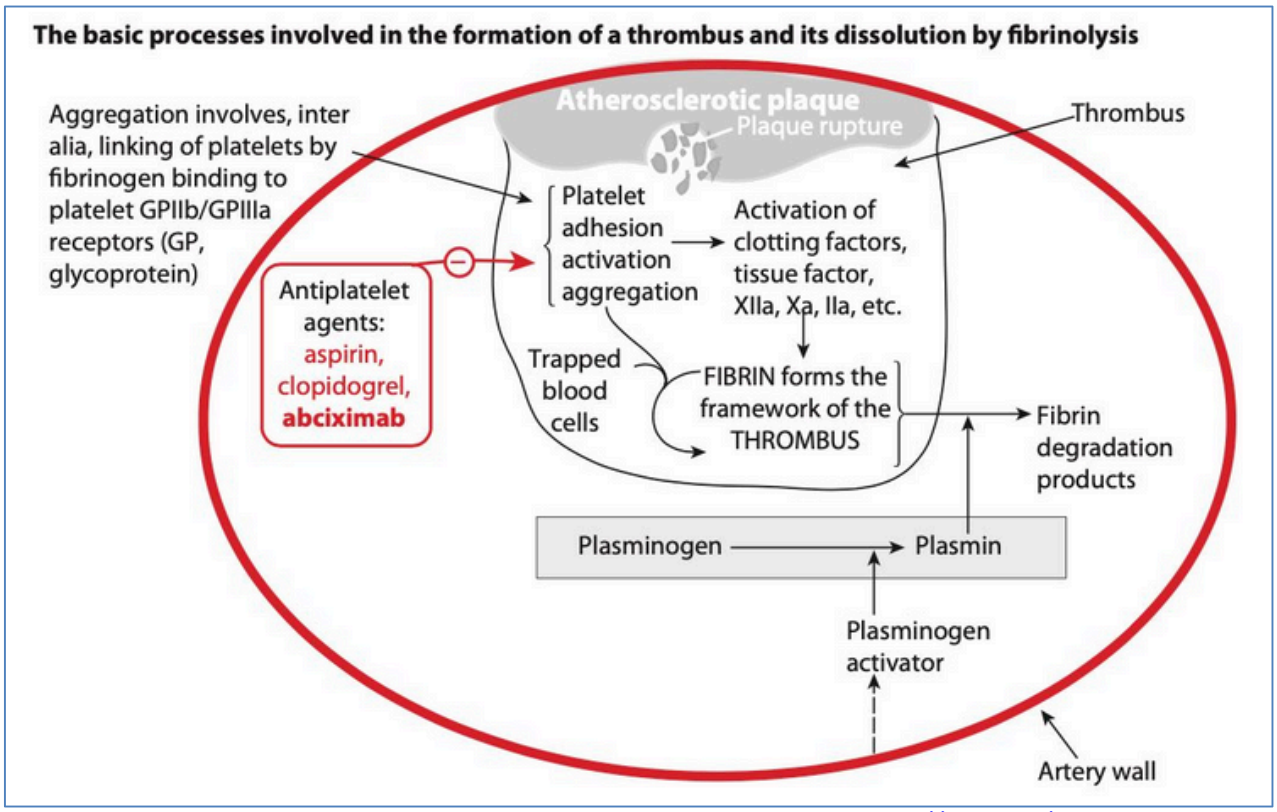
- **Indications:**
  - Secondary Prevention of Ischaemic Stroke
  - Secondary Prevention of Transient Ischaemic Attacks (TIAs – 'Mini strokes')
- **Side Effects:**
  - Headache
  - GIT Disturbances
  - Hypotension
  - Allergy

- **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
      - (Note: Active metabolite is unknown)
    - Onset Takes ≈ 8-10 days
      Action is augmented by other Antithrombotic Drugs

- **ABCIXIMAB:**
  - **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
    - Thrombocytopenia
  - **Other Information:**
    - Note: The name is simply the 'well number' + MAB (monoclonal antibody)



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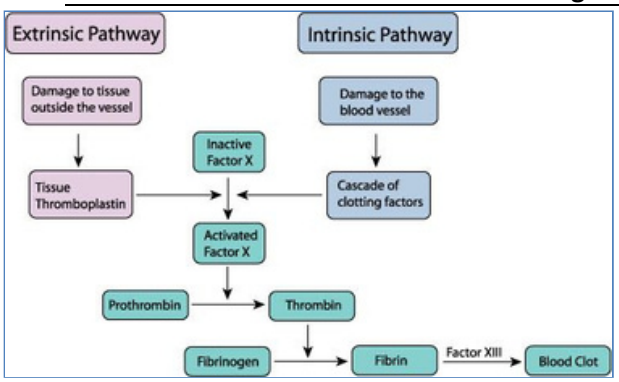
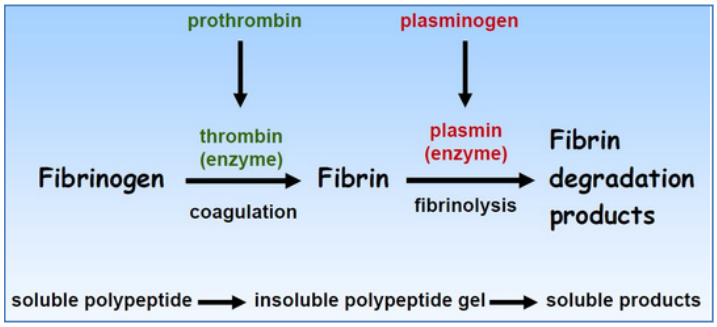
THROMBOLYTICS:

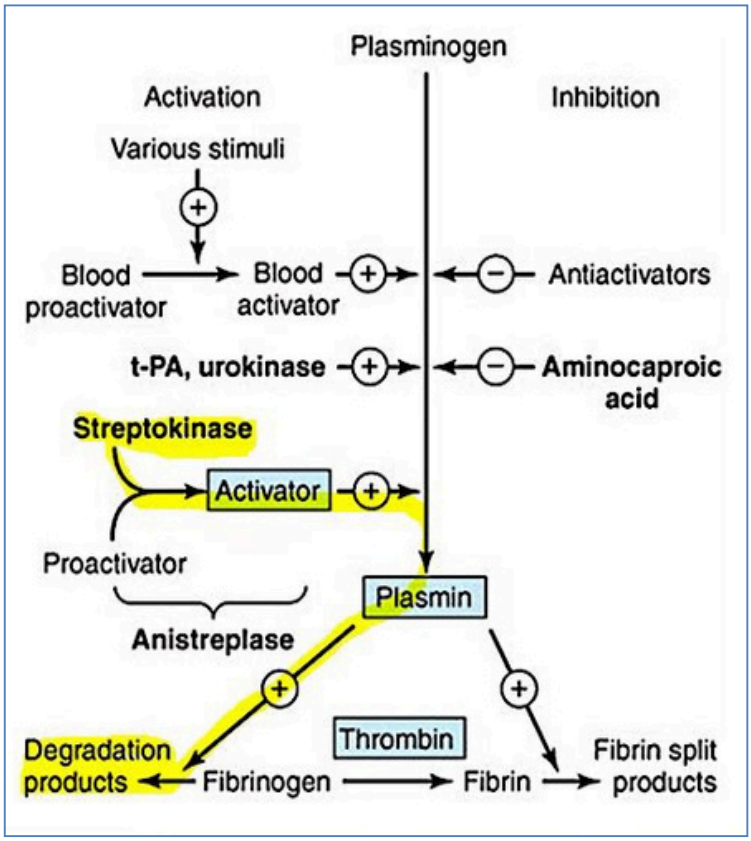
- **Note: Schematic of Fibrin Formation & Degradation:**





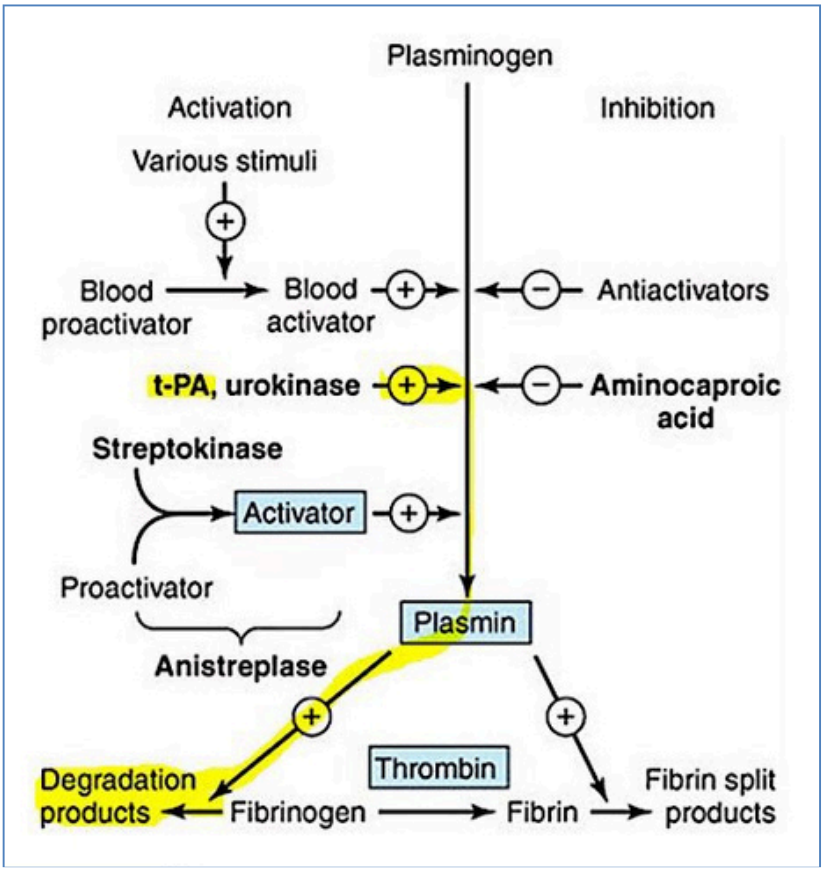
- **Streptokinase:**
  - **Mechanism of Action:**
    - An exogenous Plasminogen Activator (Catalyses conversion of Plasminogen to Plasmin)
      - → Plasmin Degrades Fibrin
  - **Indications:**
    - Thrombolysis of Inappropriate Blood Clots:
      - Pulmonary Embolism
      - Myocardial Infarction
      - Stroke
  - **Side Effects:**
    - Risk of Haemorrhage

  Other Info:
    - Derived from *Haemolytic*-Streptococci Bacteria
    - *Inhibited by Lipoproteina (an endogenous lipoprotein now considered a risk factor for MI)

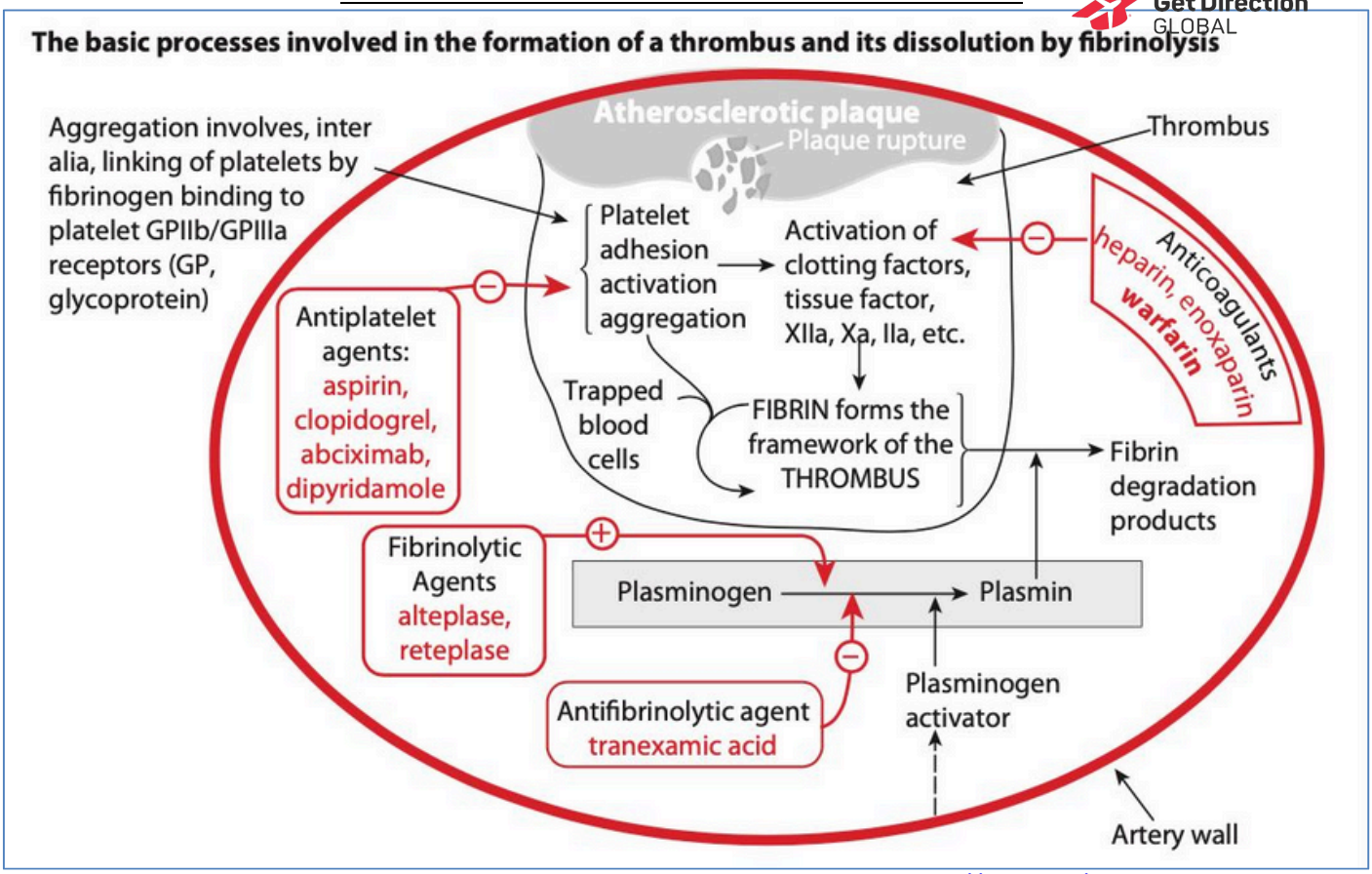


- ***(Exogenous) Recombinant* Tissue Plasminogen Activator (r-tPA):**
  - **Note: Tissue Plasminogen Activator (tPA) is normally a protein expressed on Endothelial Cells lining *Undamaged* Blood Vessels:**
    - Its role is to prevent inappropriate fibrin-clot formation in *Intact* Vessels
    - ***However,* 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 Lipoproteina (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:



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