

CLINICAL HAEMATOLOGY

NOTES

FOURTH EDITION

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

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



109 PAGES



A Message From Our Team

Studying medicine or any health-related degree can be stressful; believe us, we know from experience! The human body is an incredibly complex organism, and finding a way to streamline your learning is crucial to succeeding in your exams and future profession. Our goal from the outset has been to create the greatest educational resource for the next generation of medical students, and to make them as affordable as possible.

In this fourth edition of our notes we have made a number of text corrections, formatting updates, and figure updates which we feel will enhance your study experience. We have also endeavoured to use only open-source images and/or provide attribution where possible.

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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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BLOOD: AN OVERVIEW

BLOOD: AN OVERVIEW

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:

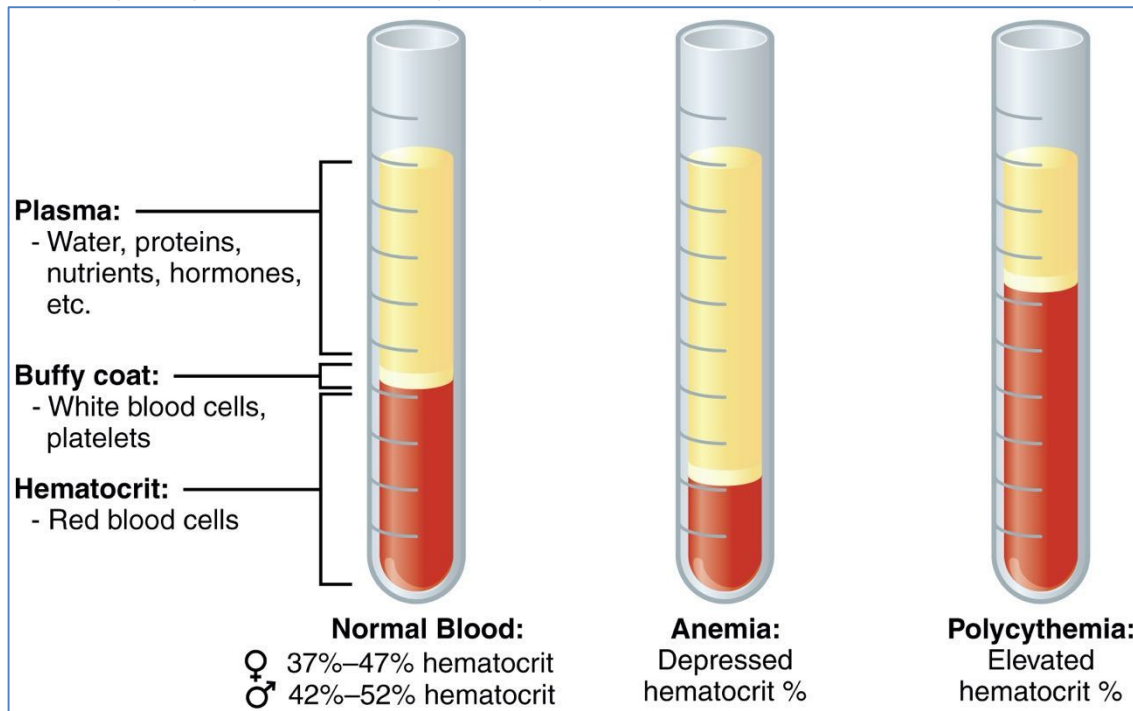
- **Distribution:**
 - Oxygen
 - Metabolic Waste
 - Hormones
- **Regulation:**
 - Temperature
 - Maintaining pH in body tissues
 - Fluid volume in Circulatory System
- **Protection:**
 - Preventing blood loss – clotting
 - Preventing infection

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




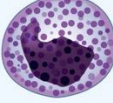



Blood Components:

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



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

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

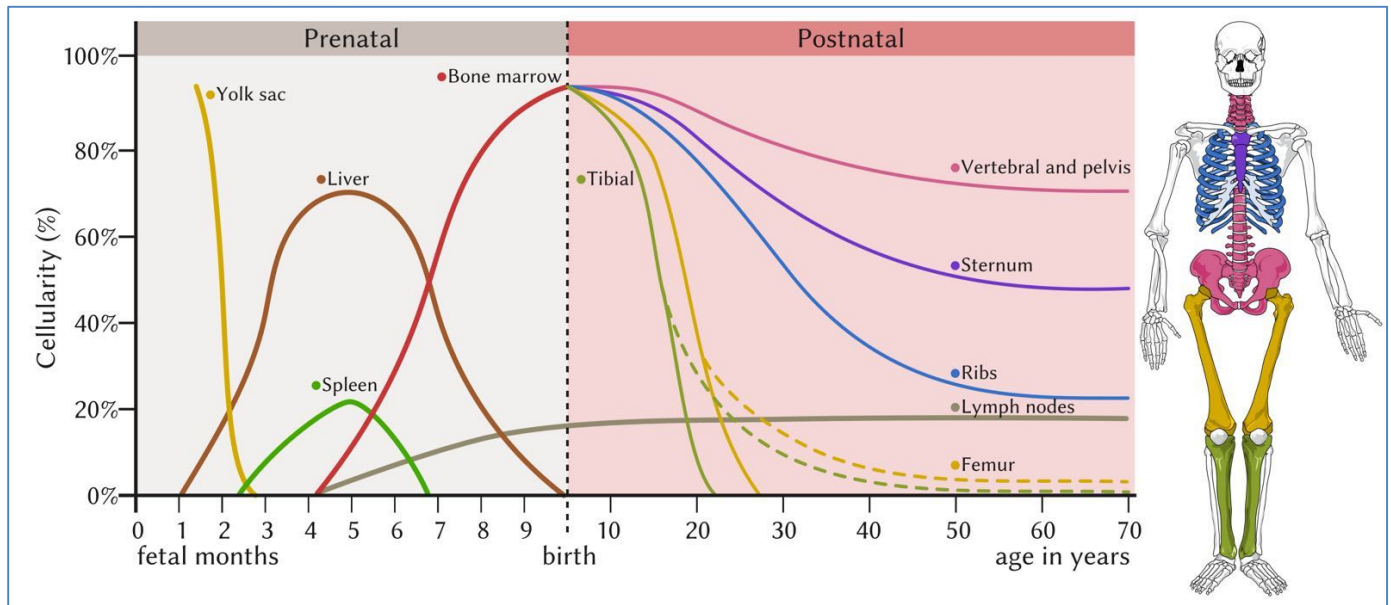
HAEMATOPOIESIS

HAEMATOPOIESIS

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

Haematopoiesis:

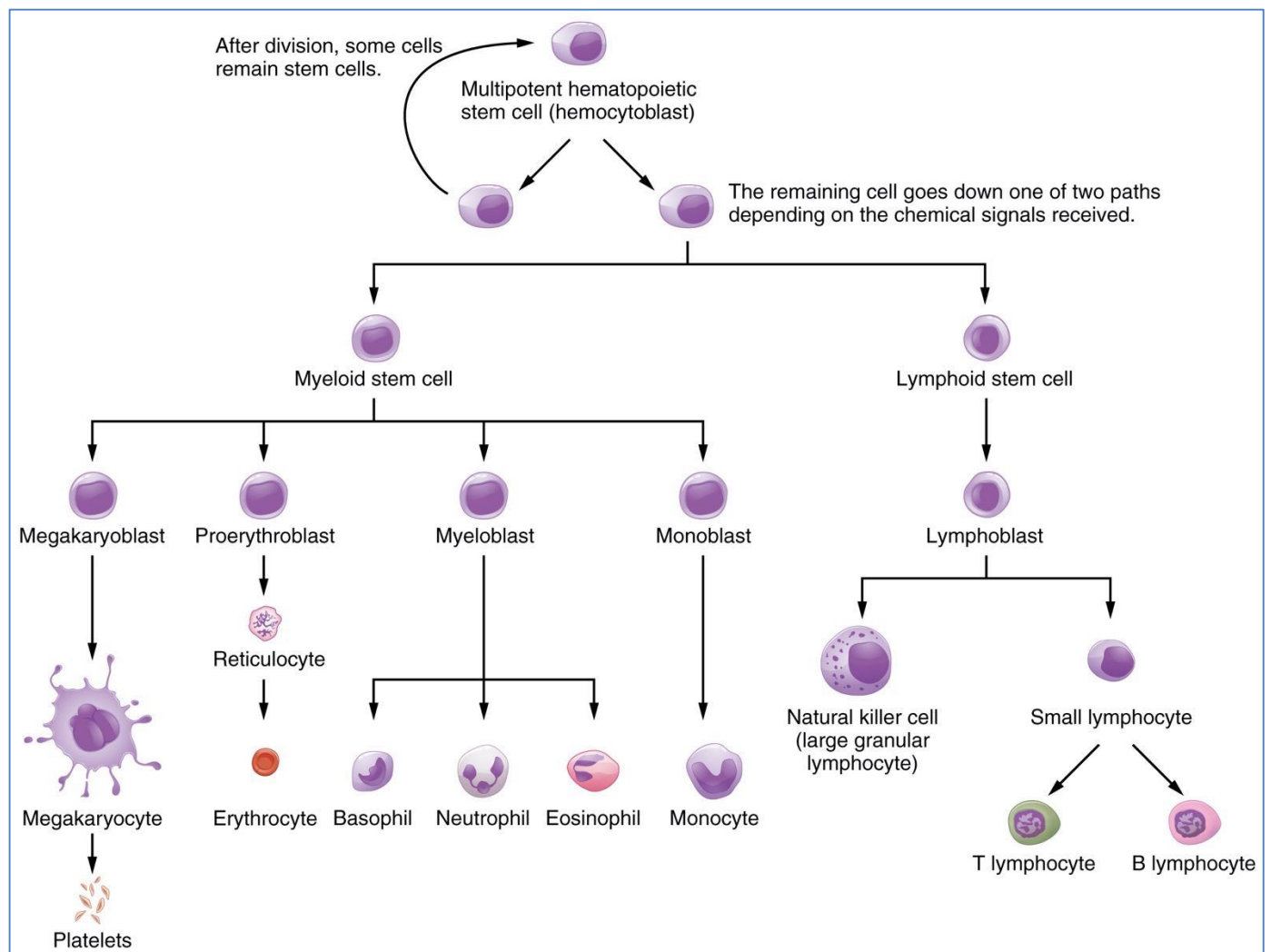
- **What is it?**
 - o = 'The Formation of Cells in the Blood from **Pluri-Potent Stem Cells**'
- **Why is it important?**
 - o Blood cells don't live forever
 - o Blood cells get used up/killed/broken down/sacrificed constantly
 - o The body needs a way to balance this blood cell turnover with new production
 - o 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?**
 - o **In Foetal Life:** Takes place in the Yolk Sac/Liver/Spleen/ & Bone Marrow
 - o **After Birth:** Takes place only in the **Bone Marrow** (Medullary Cavity)
 - I.e: 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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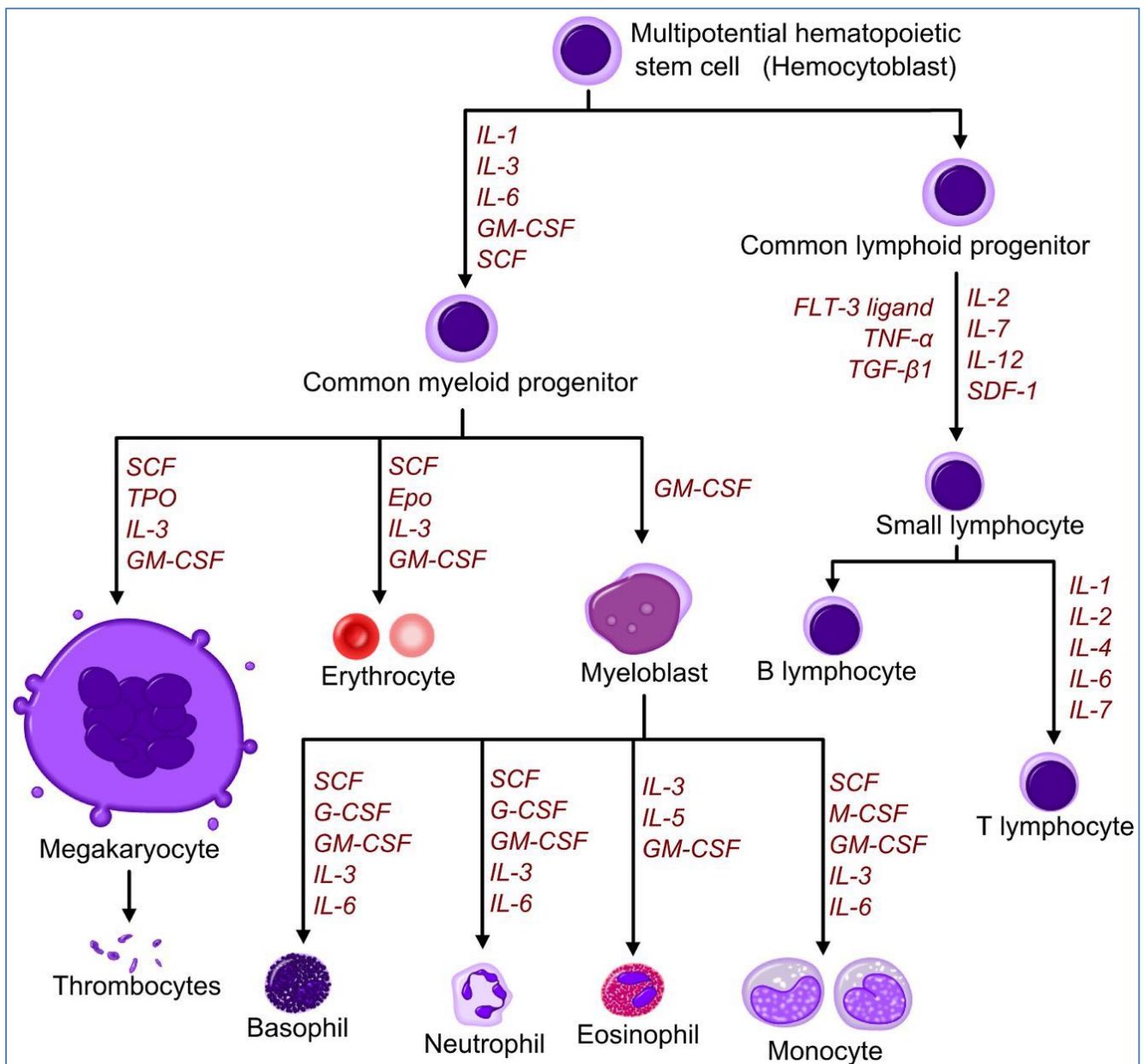
ALL Blood Cells Start As Haematopoietic Stem Cells:

- Haematopoiesis starts with **PluriPotent Stem Cells** in the bone marrow
- Stem Cells are Self-renewing
- **Cell Lineages:**
 - **Myeloid Stem Cells:**
 - **Erythroid:**
 - Proerythroblast → Reticulocyte → **RBCs**
 - **Granulocytic:**
 - Myeloblasts → **Neutrophils**
 - Eosinophilic Myeloblast → **Eosinophils**
 - Basophilic Myeloblast → **Basophils**
 - **Monocytic:**
 - Monoblast → **Macrophages**
 - **Megakaryocytic:**
 - Megakaryoblasts → Megakaryocytes → **Platelets**
 - **Lymphoid Stem Cells:**
 - **Lymphocytic:**
 - B-Lymphoblasts → **B-Cells**
 - T-Lymphoblasts → **T-Cells**
 - NK Cells
- **Considerable amplification:**
 - I.e: 1 Stem Cell can produce 10,000,000 blood cells after only 20 divisions
- **Leukemias & Lymphomas** can result from defective haematopoietic stem cell lines;
 - 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: Erythropoietin (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

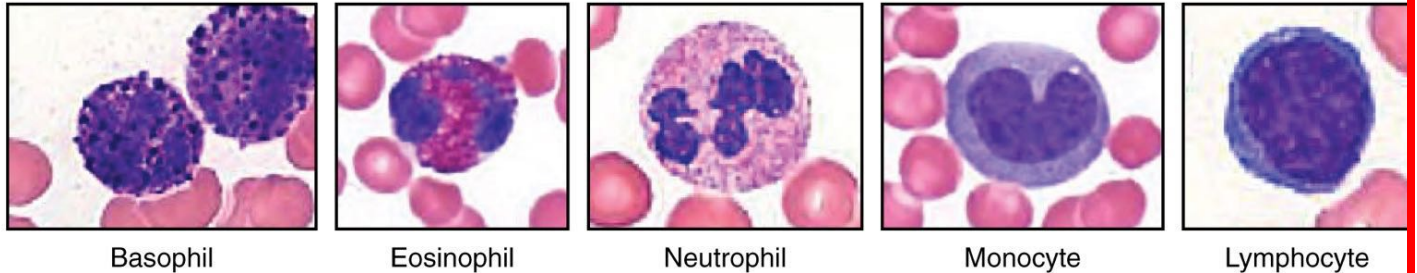


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Normal Blood Smears:

- **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

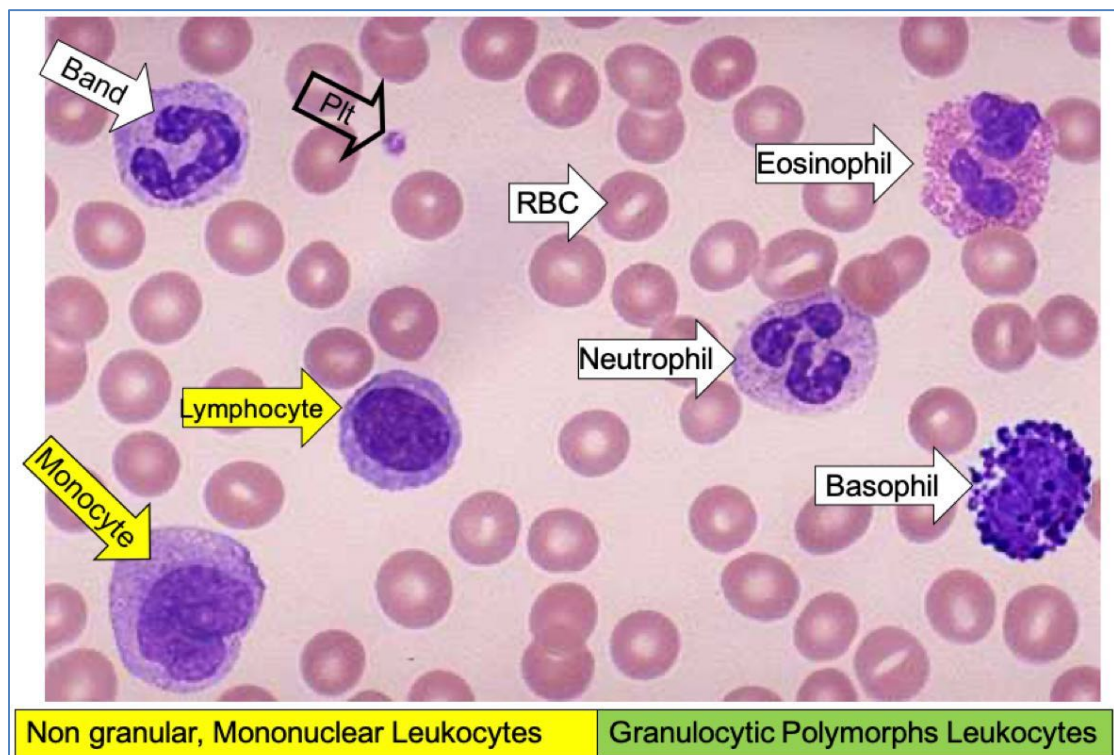
Key



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System for Looking at Blood Smears:

- (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:**

- **(Note: Philia = Too Many)**
- **(Note: Penia = Too Few)**

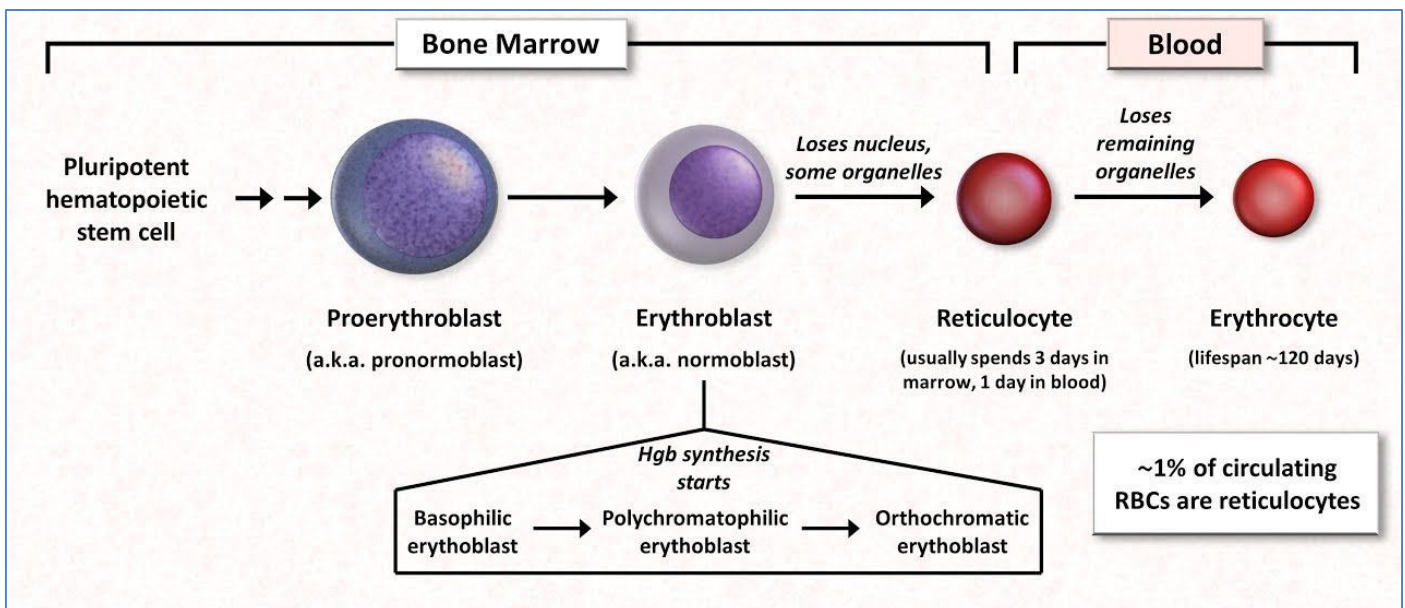
Cell Type	Causes of -Philias	Causes of –Penias
Neutrophils	Infection (bacterial, fungal) Trauma (surgery, burns) Infarction (MI, PE, Sickle-cell crisis) Inflammation (Gout, Rheum-Arthritis, IBD) Malignancy (Tumours, Hodgkin's disease) Myeloproliferative disease (Polycythaemia, CML) Physiological (Exercise,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

ERYTHROPOIESIS:

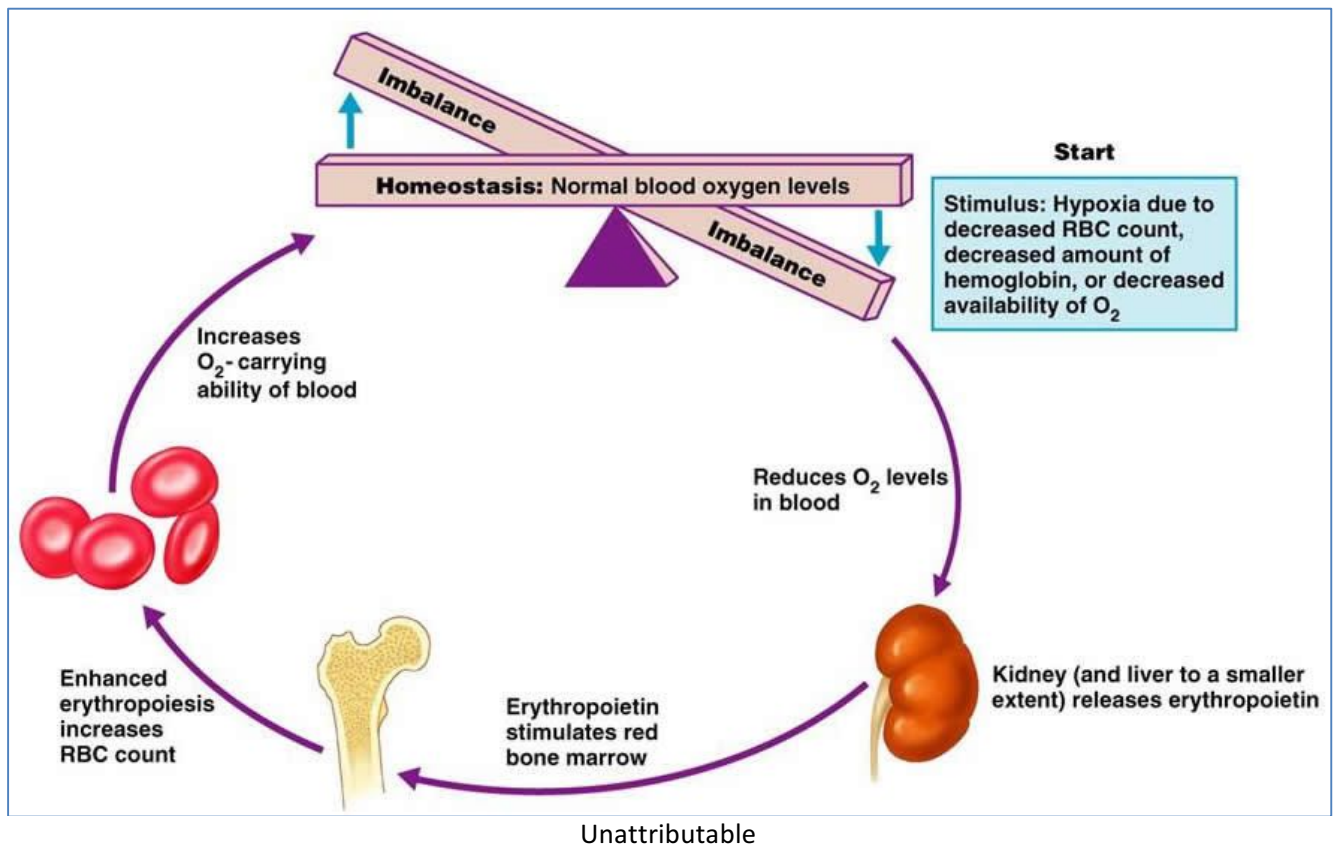
- **Erythropoiesis** = Process of **Red Blood Cell** Formation
 - o Responsible for 10^{12} new erythrocytes each day
 - o Finely Regulated
- **A similar sequence of Amplification & Maturation**
 - o **Pluripotent Stem Cells** → Pronormoblast (aka: Proerythroblast)
 - o **Pronormoblasts** → progressively smaller Normoblasts (aka: Erythroblasts)
 - o **Normoblasts** → Reticulocytes
 - o **Reticulocytes** → Mature into Erythrocytes
 - o Reticulocytes circulate in peripheral blood (1-2 days) before maturing in the *Spleen*
- **Presence of Nuclei/Organelles:**
 - o As erythrocyte precursors mature, they **gain haemoglobin & lose nuclear material**
 - o **"Blasts"** = Large, Nucleated RBC Progenitors + Organelles
 - o **"Reticulocytes"** = Smaller, Non-Nucleated RBC Progenitors (No organelles; just remnants)
- **Note: Presence of Blasts & Reticulocytes in Peripheral Blood means ↑↑ Erythropoiesis:**
 - o In a normal smear, less than 1% of RBCs are Reticulocytes
 - o **!e:** NORMALLY, All progenitors are in the marrow ONLY, except for the Erythrocyte
 - o To view *Reticulocytes*, you need "*Methylene Blue Stain*"
 - o Excess Reticulocytes can indicate Anaemia (!e: The body's effort to compensate for lack of O_2)
 - o Severe Anaemia can result in immature nucleated RBC's in the blood (not good)



Source: Unattributable

ERYTHROPOIETIN:

- Erythropoiesis is regulated by the **Hormone 'Erythropoietin'**
- **Produced by the PeriTubular Interstitial Cells of the Kidneys (Also produced by liver <10%)**
 - o Erythropoietin Production – regulated by Oxygenation of Tissues in Kidneys
 - o **Therefore Production INCREASES when:**
 - Body is Anaemic
 - Haemoglobin isn't giving up O_2 normally (Eg: Carbon Monoxide Poisoning)
 - Atmospheric $[O_2]$ is low
 - Damage to Renal Circulation (!e: Ischemia of Kidney)
 - o **Production DECREASES when:**
 - Tissue Oxygenation is Normal

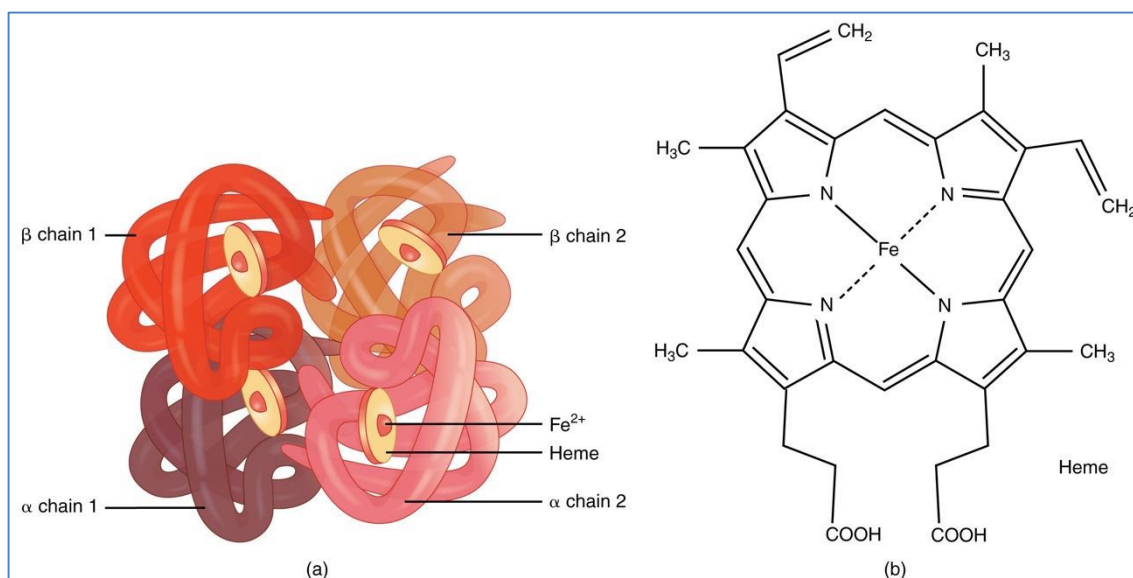


Requirements for Erythropoiesis & Haemoglobin Formation:

- The Marrow requires other precursors for effective erythropoiesis: Eg:
 - **Metals:**
 - Iron – essential for Haemoglobin synthesis
 - Cobalt
 - **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
 - **Amino Acids:**
 - For the production of cell proteins
 - **Hormones:**
 - **Erythropoietin**
 - Androgens
 - Thyroxine
 - Interleukin-3
 - GM-CSF (Granulocyte & Macrophage – Colony Stimulating Factor)

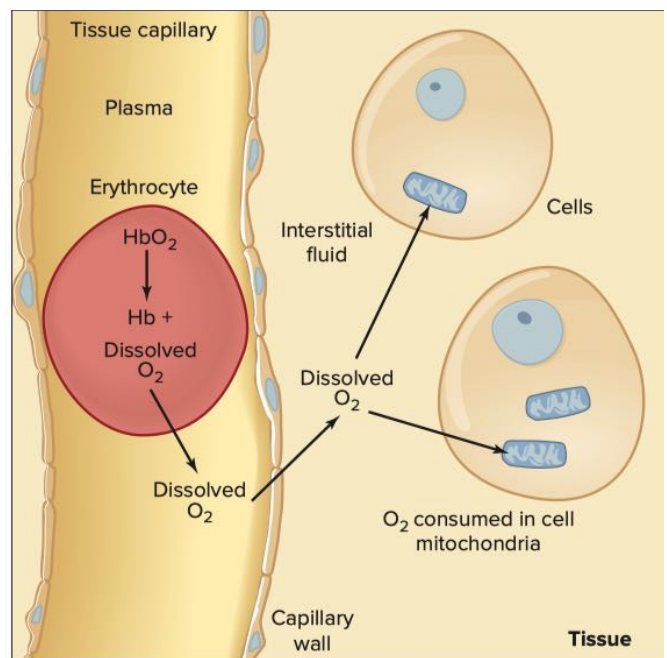
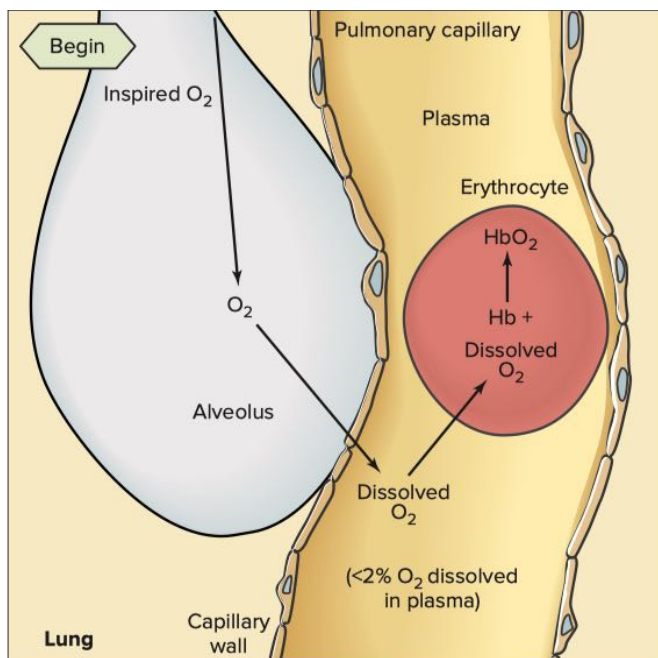
HAEMOGLOBIN:

- **Functions:**
 - To carry O_2 to tissues
 - To Return CO_2 from tissues → Lung
 - Storage pool of Iron (65% of bodily Iron is in Haemoglobin)
- **Constituents:**
 - Made up of the protein **Globin** bound to the red **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

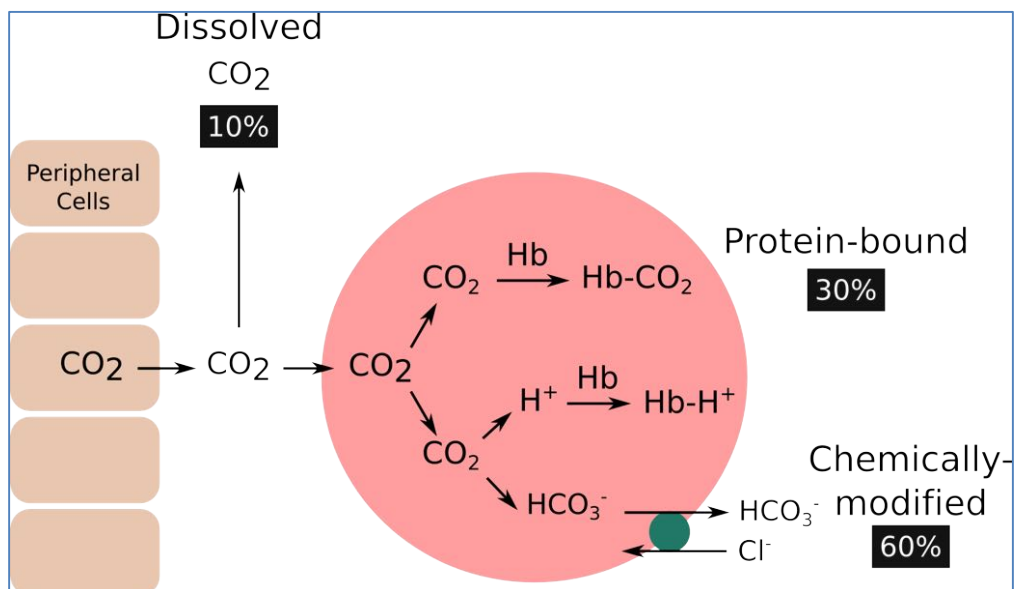


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- **Oxygen Loading:**
 - In lungs
 - O_2 diffuses into blood → into erythrocytes → binds to Iron Molecules in Haemoglobin
 - Haemoglobin → Becomes **OxyHaemoglobin**:
 - Assumes a new 3D shape
 - Becomes Ruby Red
- **Oxygen UnLoading:**
 - In Tissues
 - O_2 detaches from Iron Molecules in Haemoglobin → Out of RBC, into blood → O_2 into Tissue
 - OxyHaemoglobin → Becomes **DeOxyHaemoglobin**:
 - Resumes its former 2D shape
 - Becomes **Dark Red**
- **CO_2 Transport:**
 - CO_2 binds to Globin's Amino Acids; Rather than on the Haem Group



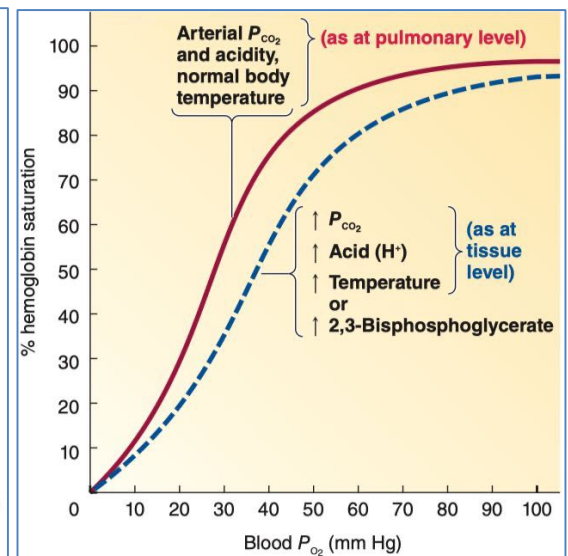
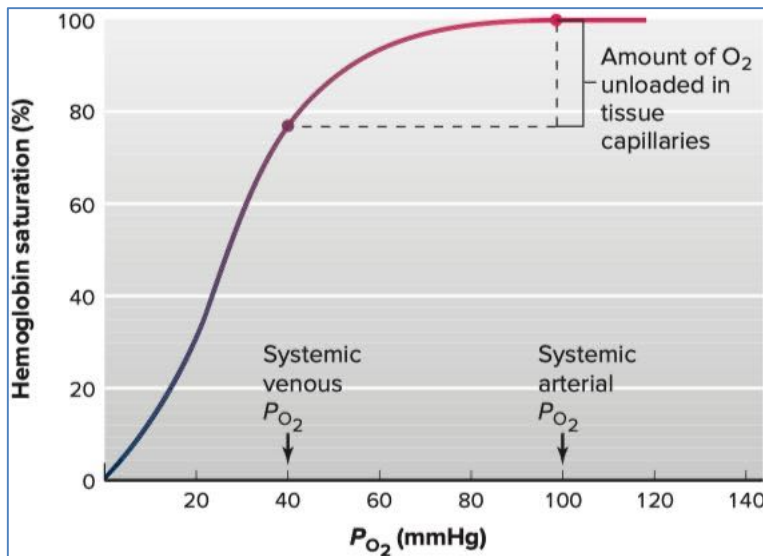
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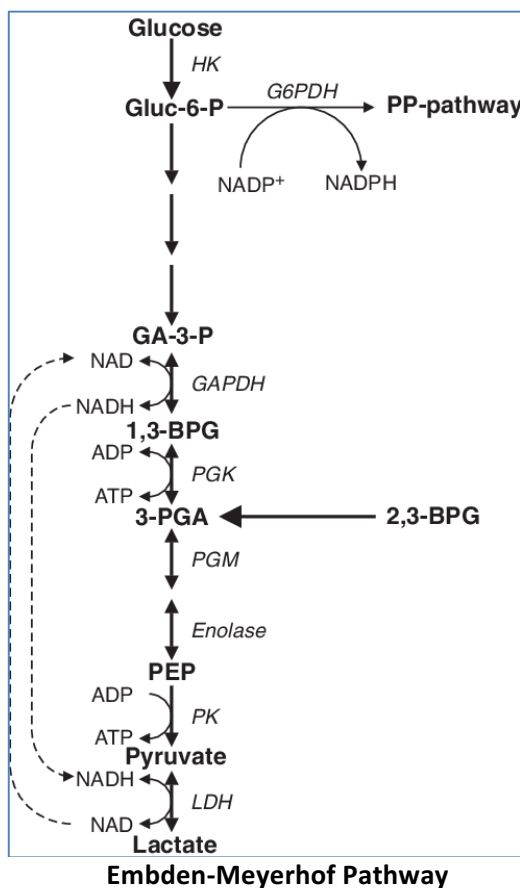
HAEMOGLOBIN – OXYGEN DISSOCIATION CURVE:

- Oxygen exchange operates between 95% Saturation (Arterial Blood) & 70% Saturation (Venous Blood)
- P_{50} = Partial Pressure of O_2 at which Haemoglobin is $\frac{1}{2}$ saturated with O_2 (Approx 26 mmHg)
- As the curve *shifts to the right*, O_2 is given up *More Readily* to the Tissues
- During CO_2 Unloading in the lungs, the curve *shifts to the left*, $\rightarrow O_2$ uptake increases

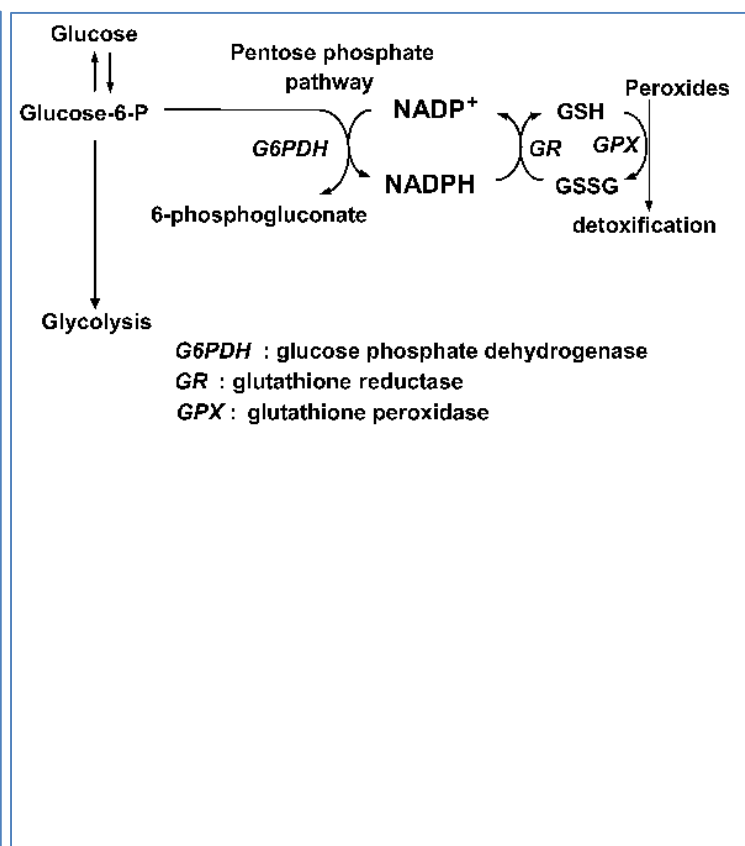


ERYTHROCYTE METABOLISM:

- *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* (Fe^{2+})
 - Iron in the *Ferric Form* is useless because it doesn't bind oxygen \rightarrow Leads to Oxidative Stress



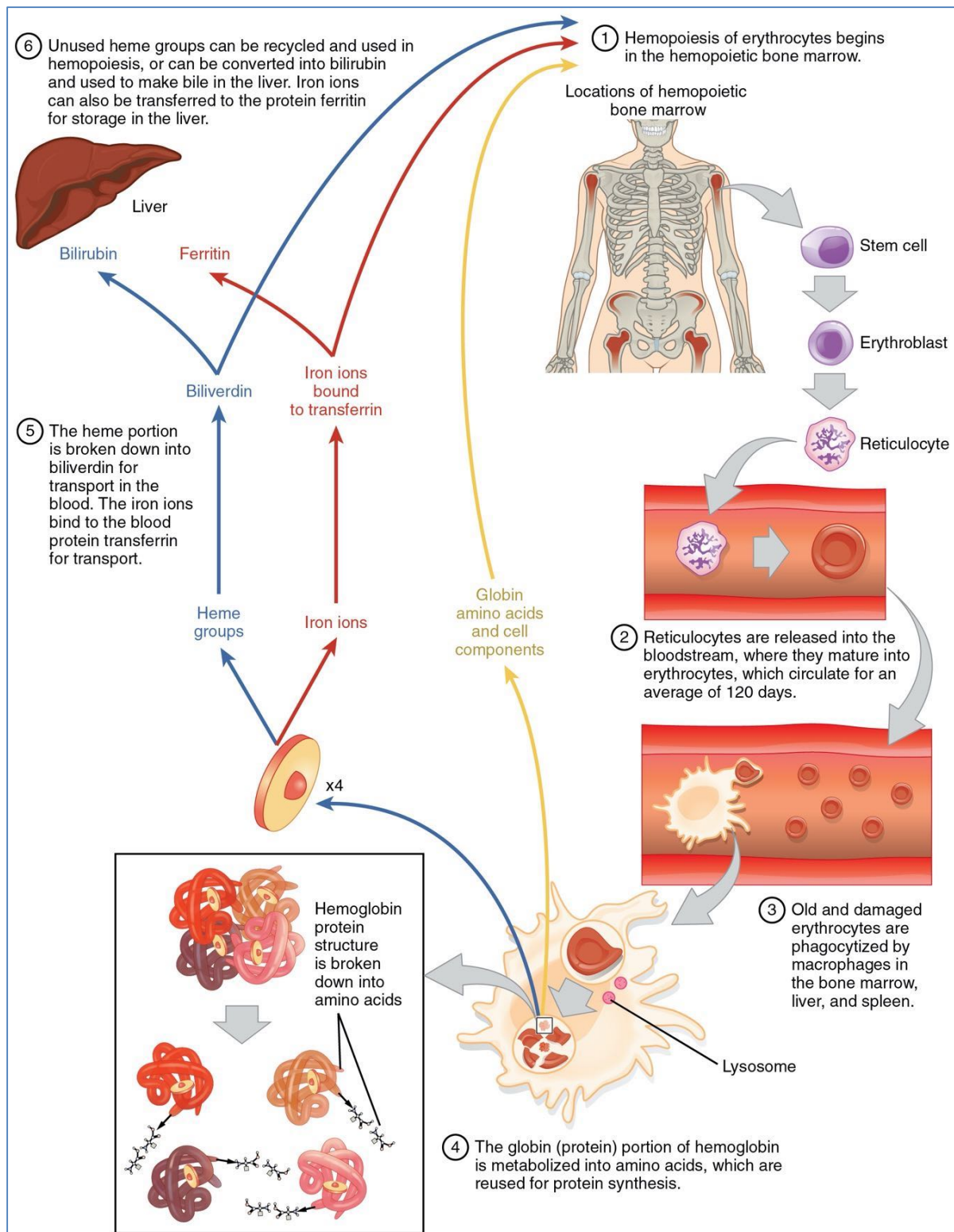
Embden-Meyerhof Pathway



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

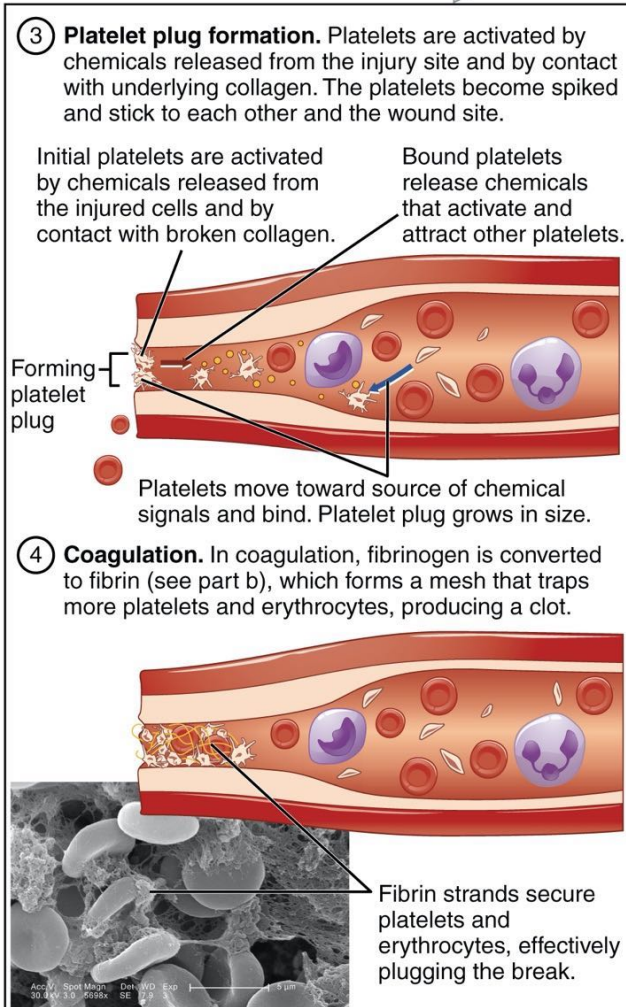
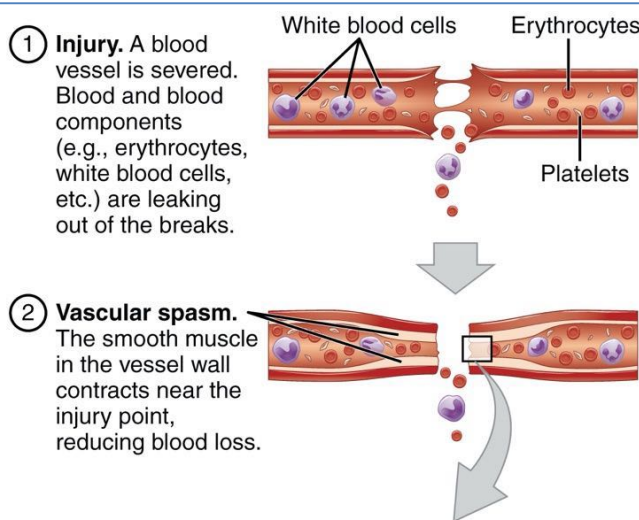


HAEMOSTASIS/HEMOSTASIS:

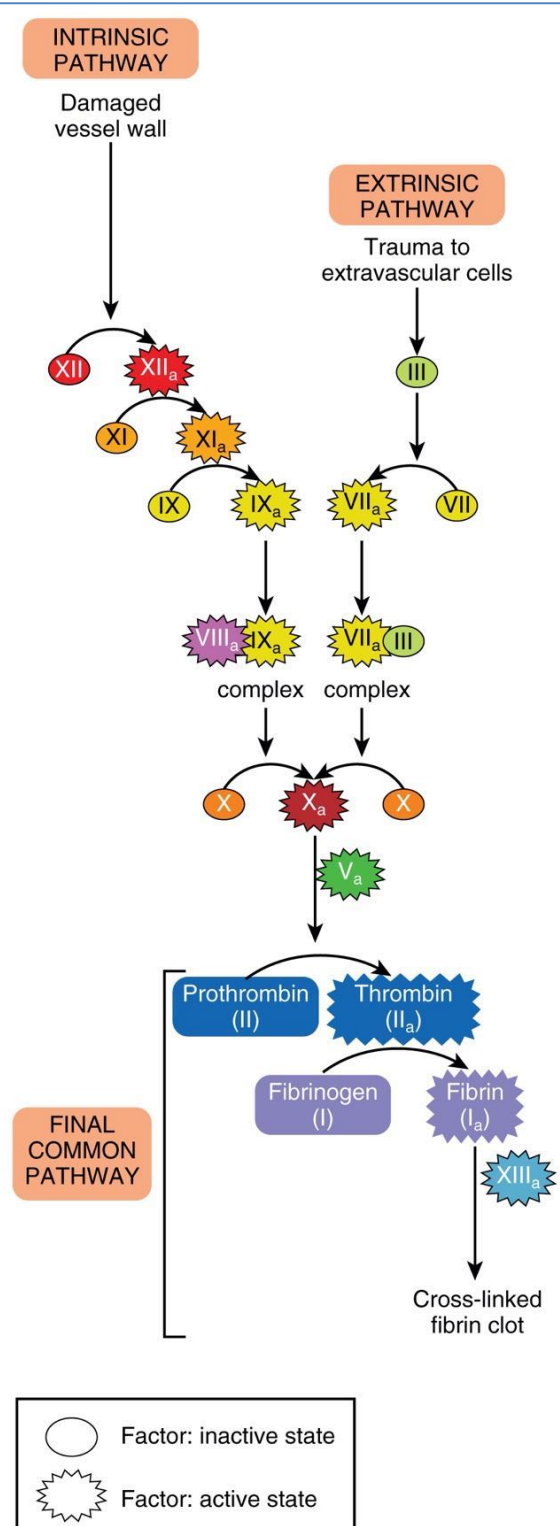
HAEMOSTASIS/HEMOSTASIS:

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 Involves a chain reaction of 12 *Blood Coagulation FACTORS* (Procoagulants)
 - o Plus Fibrin Stabilising Factor (FSF)
 - o Also involves some other substances released by platelets and injured tissue cells
- Results in a stable ‘Platelet Plug’ (clot) at the site of injury



(a) The general steps of clotting

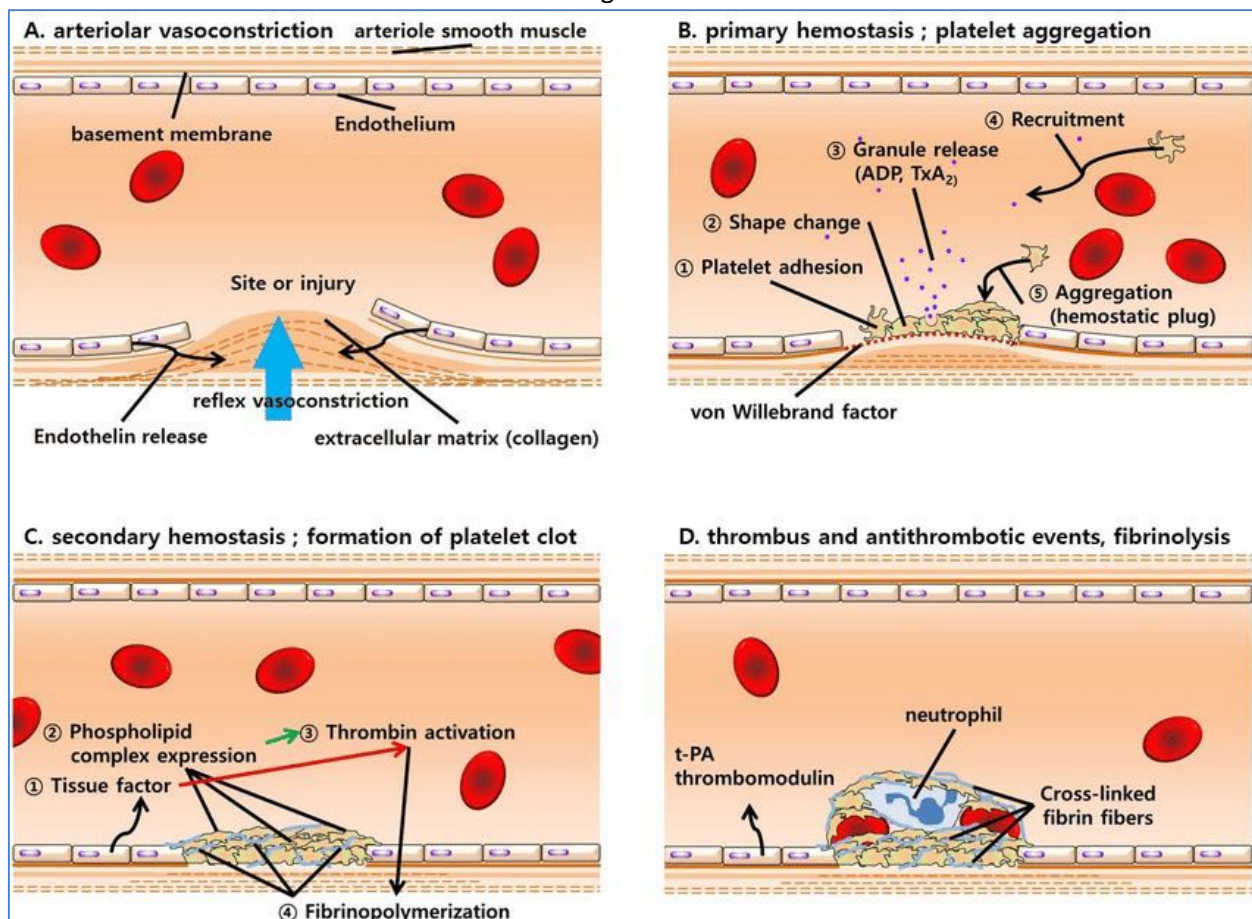


(b) Fibrin synthesis cascade

Important Components of Haemostasis:

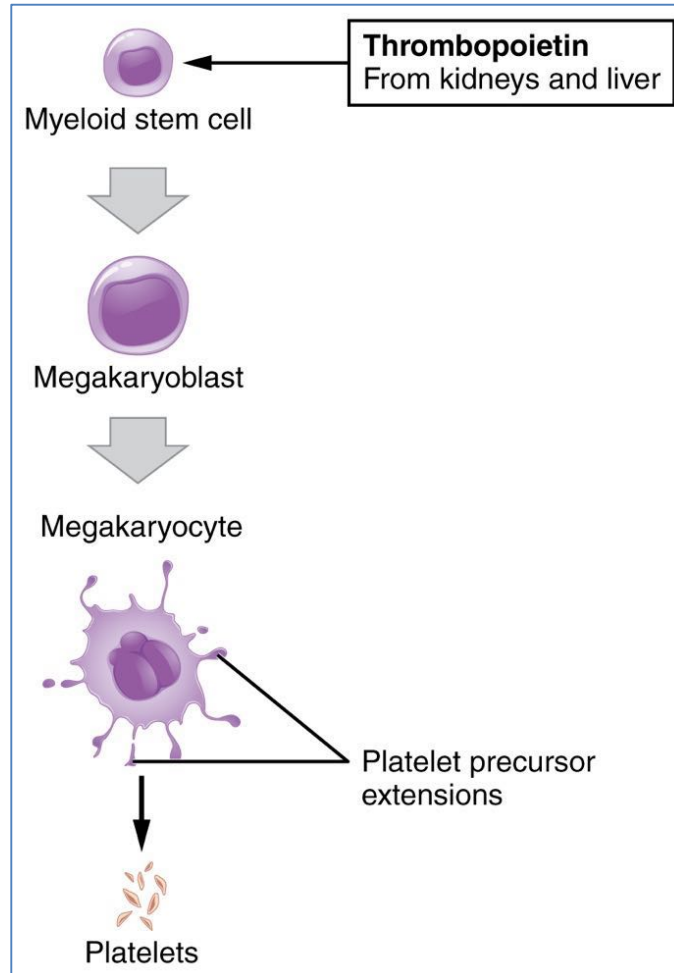
- Endothelial Cells:

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



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



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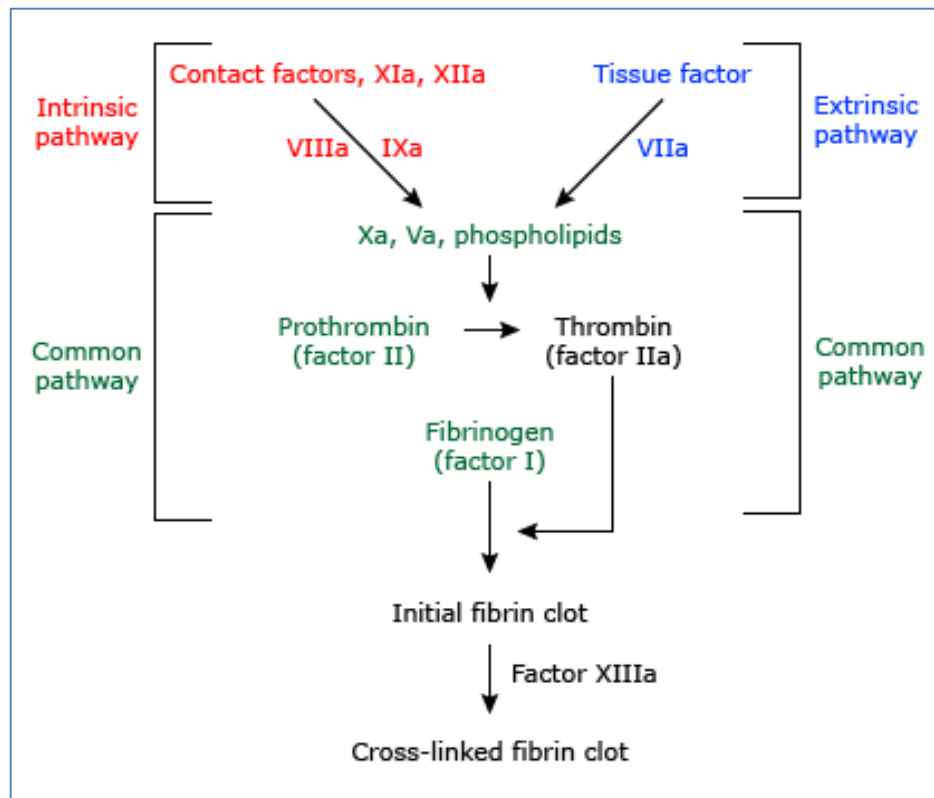
- **Coagulation Factors (Cascade):**

- **Role:** To stabilise primary platelet plug
 - Protects plug from being washed away by flowing blood
- **Dependant on Coagulation Factors**
 - Mainly produced in liver; (Some severe liver diseases → clotting deficiencies)
- **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)

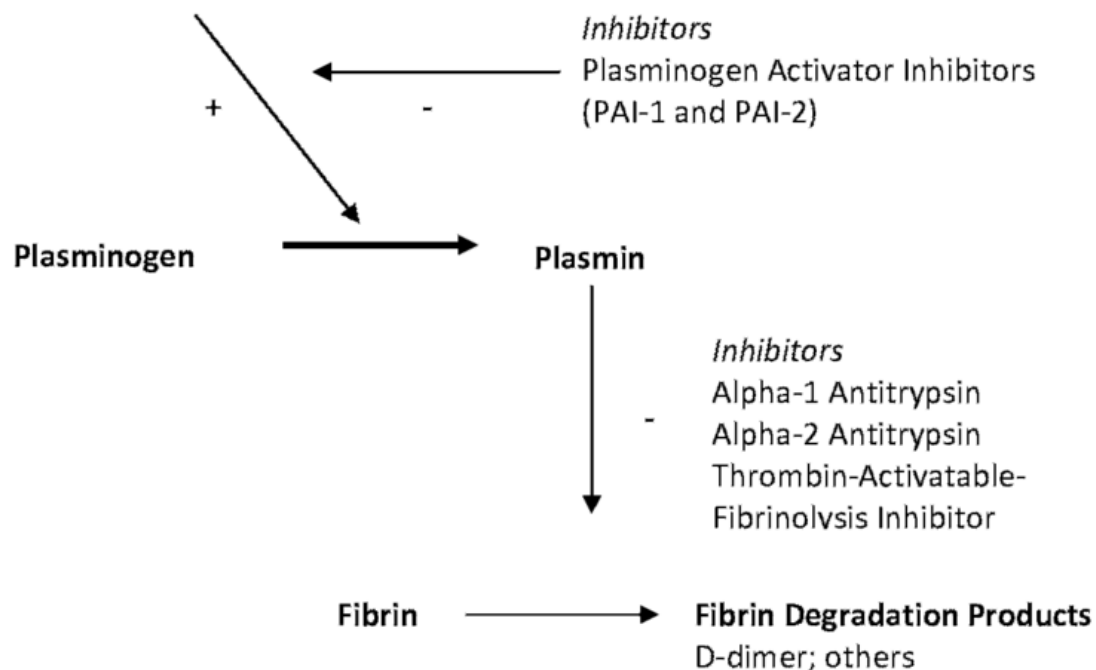
- **Plasminogen/Plasmin (Responsible for Fibrinolysis):**

- Clots aren't permanent solutions to vessel injuries
- ∴ Fibrinolysis removes un-needed clots after healing has occurred...by:
 - Blocking Coagulation Cascade:
 - & By Breaking Down Fibrin:

Activators

Urokinase-type Plasminogen Activator

Tissue-type Plasminogen Activator



3 PHASES OF HAEMOSTASIS:

PHASE 1- PRIMARY HAEMOSTASIS:

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

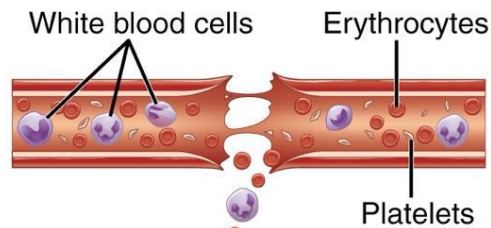
Surface Glycoproteins on Platelets

Von Willebrand Factor

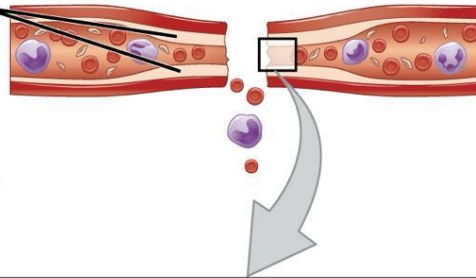
Sub-Endothelial Collagen

- c) Platelet Aggregation:
 - Once attached, Platelets → Activated → **Release Several Chemicals:**
(Platelet Activation & Secretion Enhanced by Thrombin)
 - **Serotonin:** Vasoconstrictor
 - **ADP:** Potent Platelet-Aggregating Agent
 - **Calcium (Factor IV):** A cofactor that *Activates* other *Inactive Pro-Coagulation Factors*
∴ Important in Coagulation
 - **Thromboxane A₂:** Vasoconstrictor
Potent Platelet-Aggregating Agent
 - Initiates a Positive Feedback Cycle → Activates & Attracts more & more Platelets
 - Within 1min, a platelet plug is built → further reduces blood loss
- d) Platelet-Plug Localisation:
 - **Prostacyclin:**
 - A Prostaglandin Produced by *Intact* Endothelial Cells
 - A Strong *Inhibitor* of Platelet Aggregation

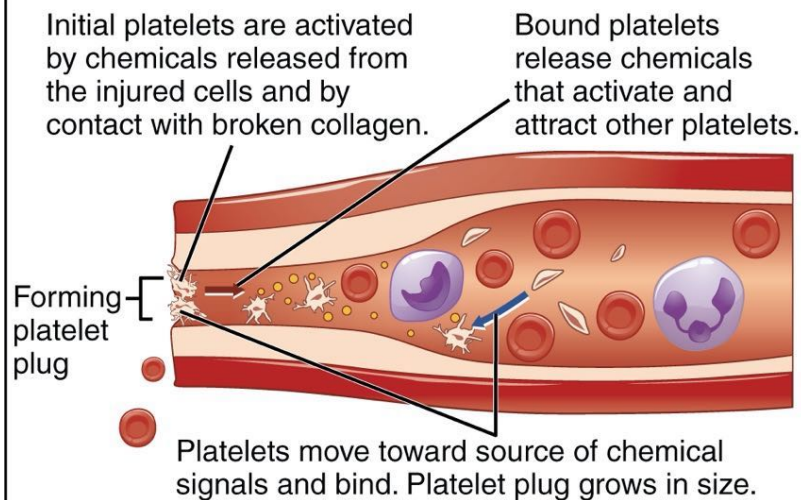
- 1 **Injury.** A blood vessel is severed. Blood and blood components (e.g., erythrocytes, white blood cells, etc.) are leaking out of the breaks.



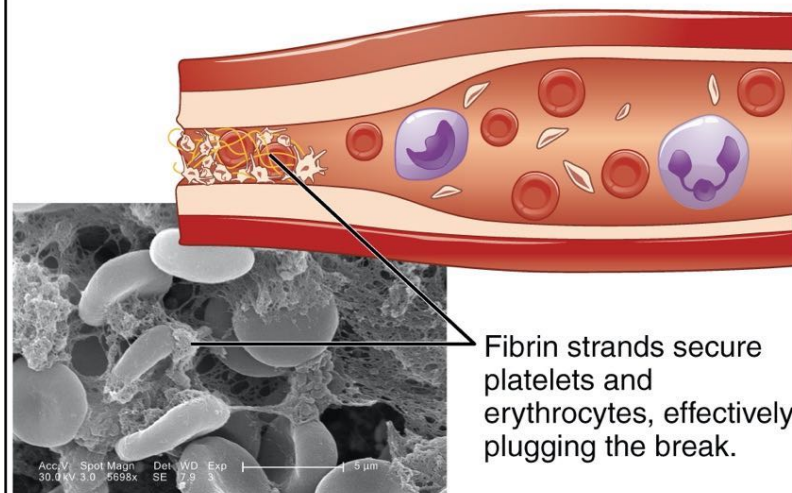
- 2 **Vascular spasm.** The smooth muscle in the vessel wall contracts near the injury point, reducing blood loss.



- 3 **Platelet plug formation.** Platelets are activated by chemicals released from the injury site and by contact with underlying collagen. The platelets become spiked and stick to each other and the wound site.



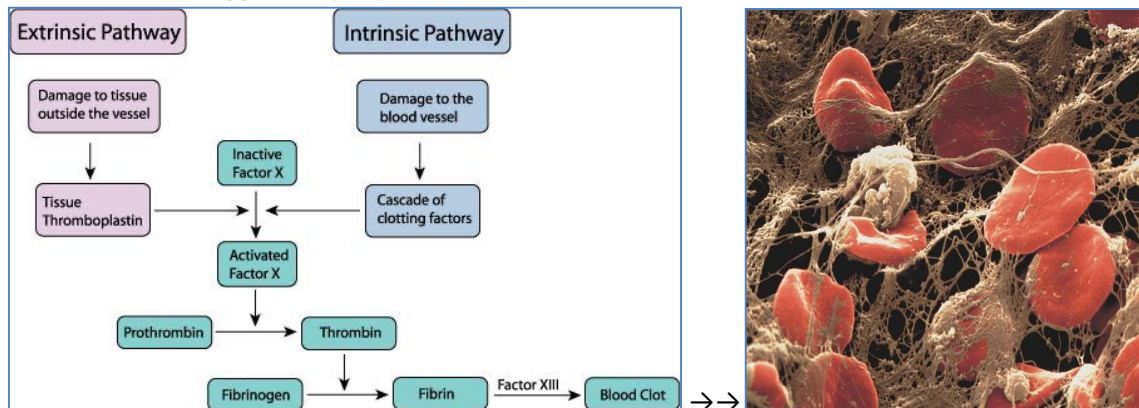
- 4 **Coagulation.** In coagulation, fibrinogen is converted to fibrin (see part b), which forms a mesh that traps more platelets and erythrocytes, producing a clot.



PHASE 2- SECONDARY HAEMOSTASIS:

a) Coagulation Cascade:

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



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:

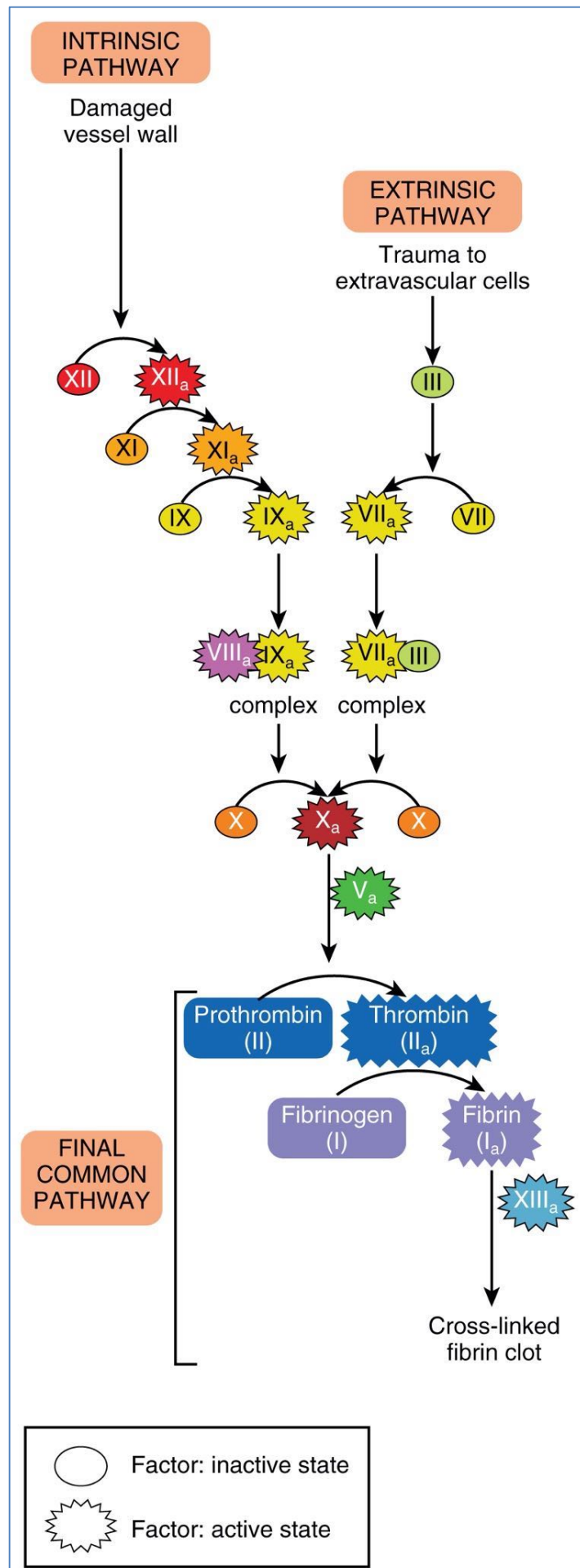
- **4- Thrombin** Catalyses Conversion & Deposition of **Fibrinogen → Fibrin**
 - Also **+Ve Feedback** on Coagulation Cascade (Amplification of Prothrombin Activation)
- **5- Fibrin Mesh** → + **Active Factor-XIII** → Stabilises the Platelet-Plug → Seals the hole
 - **Primary Platelet Plug + Mesh → Secondary Platelet Plug**

c) Regulation:

- **ProCoagulants (Clotting Factors):**
 - Factors enhancing clot-formation (Factors I – XIII)
 - Most are plasma proteins (inactive) made by the liver
 - These factors Dominate in Damaged-Vessels
- **AntiCoagulants:**
 - Factors inhibiting clot-formation
 - These factors Dominate in Undamaged-Vessels

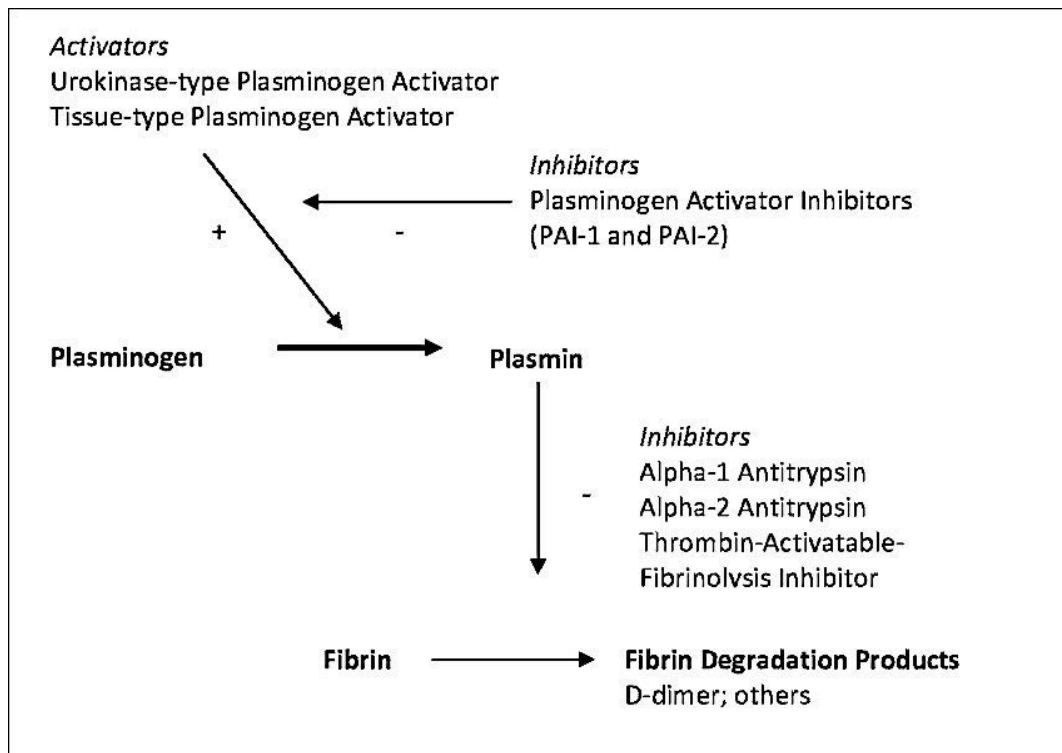
d) Coagulation Localisation:

- **Activation of Coagulation Factors is Restricted to Sites of Exposed Phospholipids:**
 - Ie: Phospholipids on platelet membranes
 - Platelet Phospholipids are exposed by Platelet-Activation
- **Anticoagulants:** See Above
 - **Tissue Factor Pathway Inhibitor:**
 - (Inhibits Extrinsic Pathway)
 - → Inactivates Factor- X_a
 - → Inhibits [Factor- VII_a – Tissue Factor Complex]
 - **Thrombomodulin:**
 - → Blocks Coagulation Cascade
 - → Binds Thrombin – Fibrinogen can't convert to Fibrin
 - → Then Activates Protein-C
 - **Protein C & Protein S:**
 - → Combine to *Inactivate* Factor- V_a & Factor- $VIII_a$
 - **Antithrombin (+ Heparin):**
 - → Inhibits Thrombin
 - → Inhibits Factor- X_a & Factor- XI_a

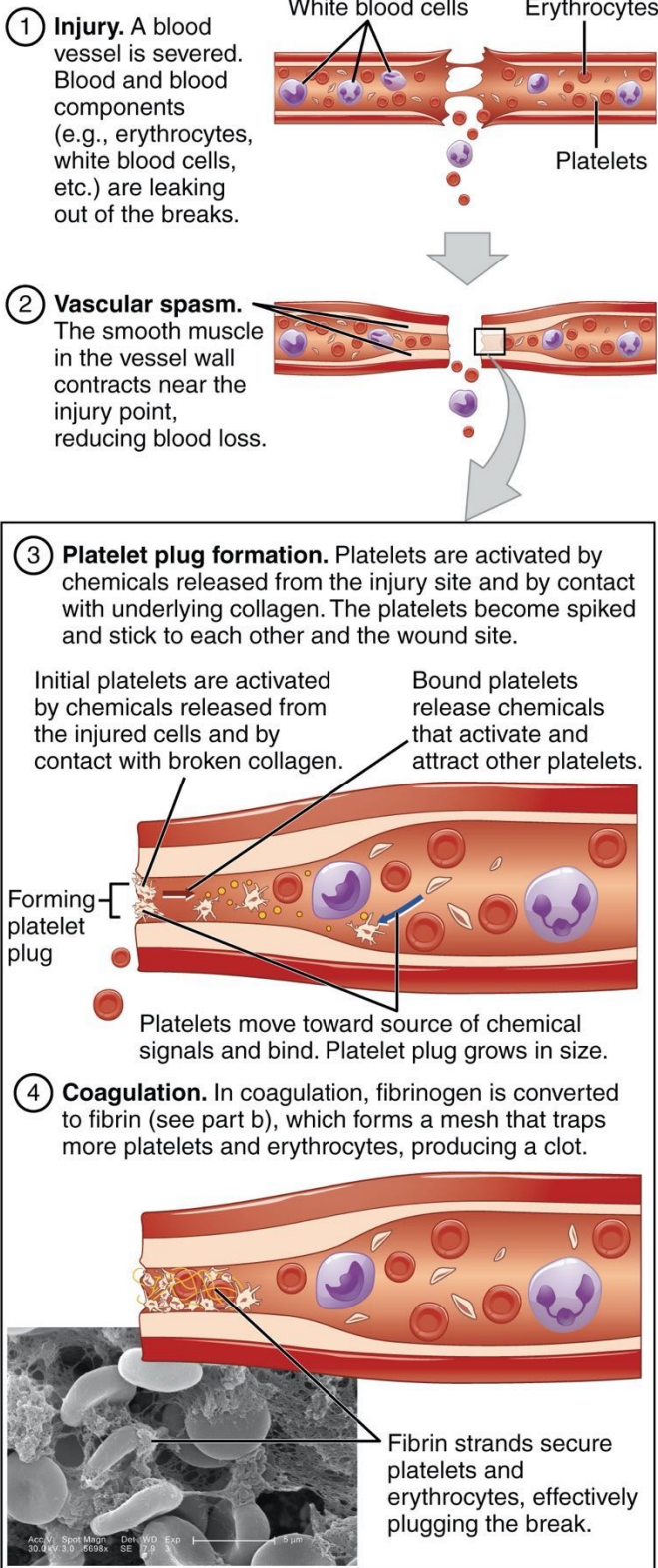


PHASE 3- FIBRINOLYSIS:

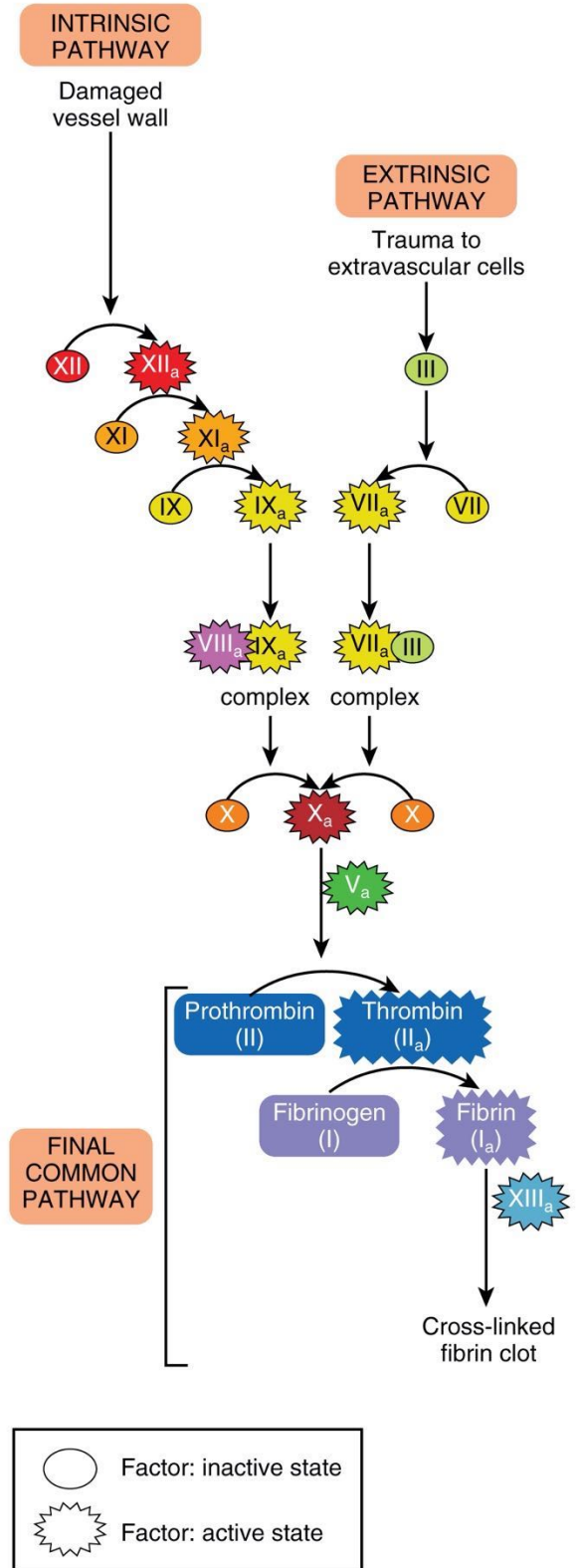
- Clots aren't permanent solutions to vessel injuries
- ∴ Fibrinolysis removes un-needed clots after healing has occurred...by:
- **Blocking Coagulation Cascade:**
 - **Thrombomodulin:**
 - Blocks Thrombin from activating Fibrinogen ∴ No Fibrin Deposition
- **& By Breaking Down Fibrin:**
 - **Via a Fibrin-Digesting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



REVIEW OF THE WHOLE PROCESS:



(a) The general steps of clotting



(b) Fibrin synthesis cascade

End of Sample

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