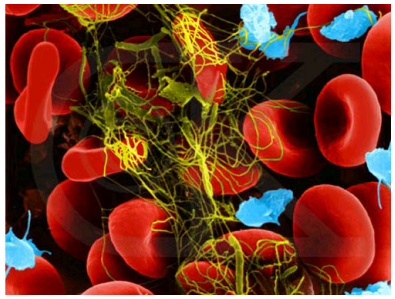
HAEMOSTASIS AND ITS DISORDERS



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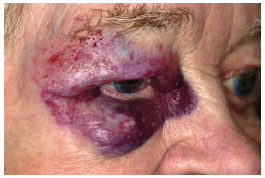
Objectives of this lecture

- Understand the term haemostasis
- Describe the role of vascular spasm in haemostasis
- Describe how a platelet plug is formed
- Describe the 3 major stages of blood coagulation including the intrinsic and extrinsic pathways
- Understand clot retraction
- Understand how a clot is replaced with fibrous tissue
- Describe some clotting abnormalities
- Understand the mechanism of action of some anticlotting drugs and other agents

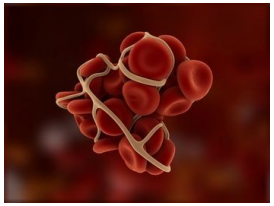
HAEMOSTASIS - to stop bleeding.

- Body's own physiological clotting mechanisms effective in dealing with small vessel injury
- Veins contain blood at a lower pressure so venous bleeding is less rapid & more easily controlled.
- A collection of blood in the tissues from any vessel type is called a haematoma.



MECHANISM OF HAEMOSTASIS

- Vascular spasm
- Formation of a platelet plug
- Formation of a blood clot through coagulation
- Clot retraction
- Replacement of the clot with fibrous tissue

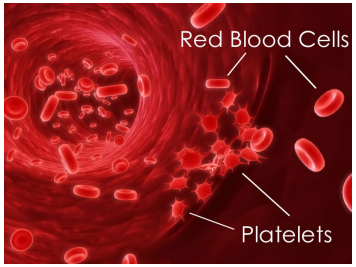


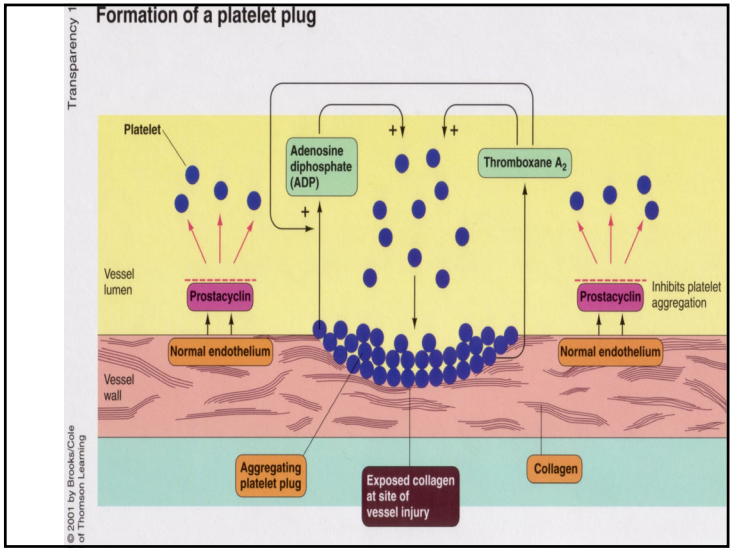
1. VASCULAR SPASM

- trauma to vessel wall → contraction.
- contraction results from
  - nervous reflexes initiated by pain
  - local smooth muscle spasm
  - local chemical factors produced by traumatised tissues.
- platelets release the vasoconstrictor substance, thromboxane A_2.
- The greater the damage, the greater the degree of spasm.
- local vascular spasm lasts many minutes or even hours

PLATELETS

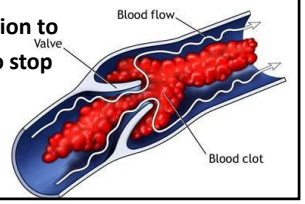
- formed in bone marrow from megakaryocytes
- round or oval 2-4μm diameter
- 200,000 – 500,000 per cubic millimeter
- contain mitochondria, smooth endoplasmic reticulum and cytoplasmic granules but no nuclei, cannot reproduce
- live for 8 days, eliminated by macrophages
- glycoprotein coat so platelets slide past normal vessel walls & stick to injured areas
- have secretory vesicles containing adrenaline, serotonin, ADP & thromboxane A_2





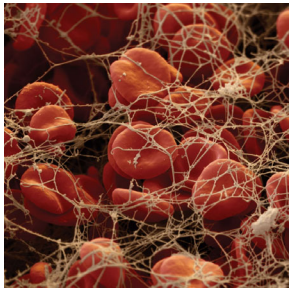
- damaged vessel disrupts endothelium & exposes connective tissue & collagen.
- platelets swell, form irregular shapes with numerous pseudopods & attach to exposed collagen - platelet adhesion.
- contractile proteins in platelets contract forcefully - release multiple active factors from storage granules.
- adrenaline & serotonin cause vasoconstriction - minimise blood loss.
- ADP causes surface of nearby circulating platelets to become sticky - adhere to first layer of platelets. These platelets also release ADP causing more platelets to pile on – platelet aggregation - platelet plug is formed.

- platelets produce thromboxane A_2 - directly promotes platelet aggregation & triggers the release of more ADP from platelet granules.
- platelet plug limited to site of vessel injury - normal endothelium releases prostacyclin - profoundly inhibits platelet aggregation
- small hole - platelet plug by itself can stop blood loss
- large hole - blood clot in addition to the platelet plug is required to stop the bleeding.



3. FORMATION OF A BLOOD CLOT THROUGH COAGULATION

- transformation of blood into solid gel or clot or thrombus
- consists mainly of protein polymer called fibrin
- clotting occurs around platelet plug
- reinforces plug

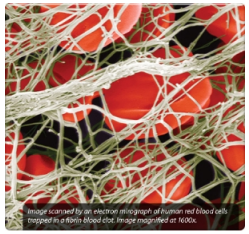


4. CLOT RETRACTION

- platelets contain actin & myosin
- pull edges of damaged vessel together
- serum (plasma minus fibrinogen) is exuded

5. REPLACEMENT OF CLOT WITH FIBROUS TISSUE

- platelets secrete a protein which stimulates growth of arterial smooth muscle & skin fibroblasts
- serotonin may play a role – stimulates secretion of collagen by fibroblasts
- clot is converted into fibrous tissue
- process takes 1-2 weeks



3. MECHANISM OF BLOOD COAGULATION

THREE MAJOR STAGES

- Injury to vessel → cascade of chemical reactions → formation of prothrombin activator
- Conversion of prothrombin to enzyme thrombin, catalysed by prothrombin activator
- Thrombin acts as an enzyme to convert fibrinogen to fibrin fibres that trap platelets, blood cells & plasma to form a clot

PROTHROMBIN ACTIVATOR

Formation of this is the rate limiting step in blood coagulation!

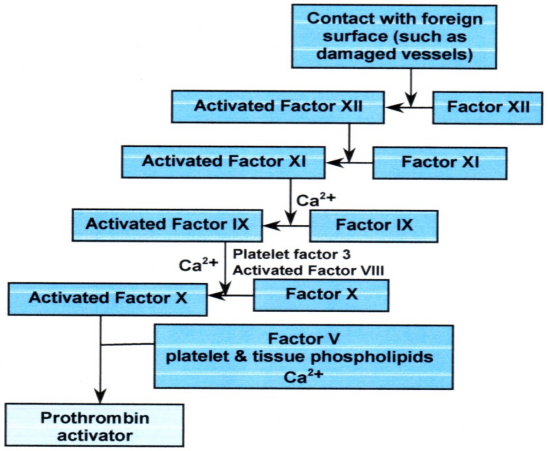
Prothrombin activator formed in two ways

- by the extrinsic pathway involving factors present in damaged tissue
- by the intrinsic pathway involving factors already present in plasma

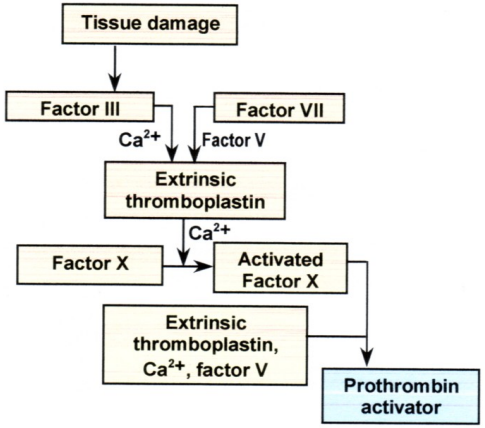
In both pathways, clotting or coagulation factors (plasma proteins) play major roles.

When active, their enzymatic actions cause the next cascading reactions of the clotting process.

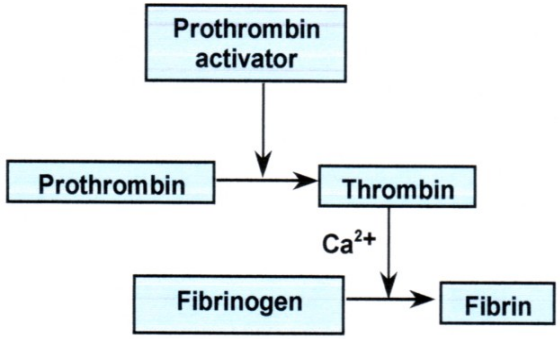
INTRINSIC CLOTTING PATHWAY



EXTRINSIC CLOTTING PATHWAY

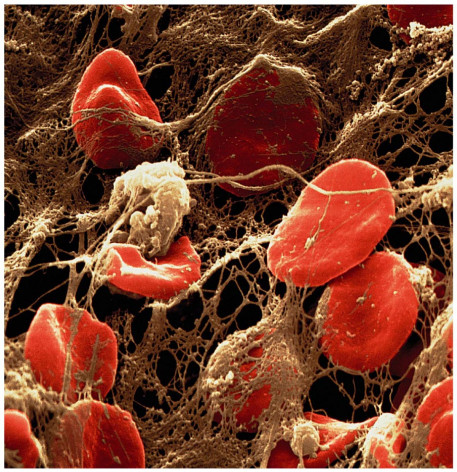


COMMON PATHWAY



CONVERSION OF FIBRINOGEN TO FIBRIN

- fibrinogen – high MW protein
- formed in liver
- plasma conc 100-700 mg/100ml plasma
- thrombin changes fibrinogen into a smaller fibrin monomer which polymerises with other fibrin monomers to form a loose network of strands held together by weak hydrogen bonds
- meshwork is then stabilised by the formation of covalent linkages between strands, a reaction catalysed by fibrin stabilising factor – adds strength to fibrin meshwork
- final clot - meshwork of fibrin fibres that entrap blood cells, platelets, and plasma
- fibrin fibres adhere to damaged blood vessels - prevent further blood loss.



DISSOLVING THE CLOT

- plasminogen – anticlotting plasma protein
- converted to active enzyme plasmin
- plasmin digests fibrin and other clotting factors

and so dissolves the clot.

Vitamin K deficiency

- vit K required for the production of several important clotting factors.
- insufficiency of vit K → serious bleeding disorders
- vit K is fat soluble
- synthesised in G.I. tract by bacteria.
- requires bile for its absorption in small intestine.
- warfarin is a competitive inhibitor of vit K.

Haemophilia

hereditary disease characterised by uncontrolled bleeding

- in 80% - due to lack of Factor VIII
- inheritance - recessive sex-linked, carried by mother on X chromosome
- severity varies - excessive bruising, persistent bleeding after simple cut, haemorrhage into joints & muscles

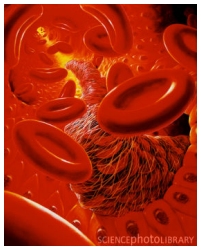
Thrombocytopenia

- low platelet numbers
- tendency to bleed
- skin - small purplish patches.
- mostly due to formation of antibodies which react against the platelets themselves to destroy them.
- autoimmunity – cause unknown

ABNORMAL CLOTTING

Thrombus

- abnormal clot in vessel
- commonly due to endothelial walls roughened by atherosclerosis or infection



Embolus

- free flowing clot
- originating in left side of heart / large arteries → stroke, renal obstruction, blindness
- originating in right side of heart / large vein→ block pulmonary arteries

ANTICLOTTING DRUGS

Oral

• aspirin – inhibits formation of thromboxane A_2, decreasing platelet aggregation and platelet plug formation

• warfarin – competitive inhibitor for Vitamin K, lowers the level of prothrombin & other clotting factors

Intravenous

• heparin – naturally occurring, produced by basophils & mast cells – inhibits formation of thrombin & reduces platelet function

• tissue plasminogen activator (t-PA) – when delivered directly to area of thrombosis, it activates plasminogen to plasmin which can dissolve clots (thrombolytic)

• streptokinase – same action as t-PA, produced by streptococci bacteria

IN VITRO ANTICLOTTING AGENTS

• silicon

• heparin – used for preventing coagulation of blood outside body as well

• Ca^{2+} binding substances (eg oxalate, citrate, EDTA)