**HAEMATOLOGY 7 & 8**

**HAEMOSTASIS AND ABNORMALITIES OF HAEMOSTASIS**

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**Learning Objectives**

The student should be able to:

• Describe the normal haemostatic mechanisms including the interactions of vessel wall, platelets and clotting factors

• Describe and distinguish the clinical features of bleeding due to thrombocytopenia and coagulation disorders, respectively

• Describe the use of laboratory tests to assess haemostasis

• Describe the principles of management of disorders of haemostasis

Haemostatic plug formation is essential to prevent blood loss from intact vessels and to arrest bleeding from injured vessels. A series of linked processes are involved:

1. Vessel constriction occurs as a local contractile response to injury. This is in itself sometimes sufficient to temporarily restrict blood loss from a wound in small blood vessels.
2. Almost immediately following vessel injury, platelets adhere to the subendothelial structures. There are a number of molecules mediating the adhesion reaction, including extravascular collagen, von Willebrand factor and membrane-glycoproteins. Activation of platelets, particularly by adenosine diphosphate (ADP) and thrombin, then results in aggregation and the formation of an unstable platelet plug.
3. Stabilisation of the unstable plug is achieved by the tissue factor activation of the blood coagulation system and formation of fibrin clot.
4. Finally, the clot is lysed by the fibrinolytic enzyme system and blood vessel repair is initiated.

Vessel disorders causing bleeding arise because of impaired interaction of platelets with the compromised vessel. Examples are scurvy, senile purpura, allergic vasculitis (acquired) and haemorrhagic telangiectasia, Ehlers-Danlos syndrome (inherited).

The platelet has its origin in the bone marrow. Haemopoeitic stem cells give rise to megakaryocyte precursers which undergo nuclear replication without cytoplasmic division, then maturation before migrating to the marrow sinusoids, extending proplatelets through the endothelial wall and fragmenting into platelets in the circulation.





The lifespan of the platelet is ~10 days, and ~1/3 of the platelets are sequestered in the spleen. An important metabolic pathway in platelets converts membrane phospholipids to thromboxane A2, which can activate platelets. Aspirin acts as an antiplatelet agent by irreversibly inhibiting one of the enzymes of this pathway, cyclo-oxygenase. ADP, released from platelet granules, and thrombin are other activators. The adhesive and aggregation reactions of platelets are mediated through surface membrane glycoproteins (Glp), Glp Ib, Glp Ia-IIa and Glp IIb/IIIa.

Platelet disorders may be acquired (common) or inherited (rare). Acquired disorders include a low platelet count (thrombocytopenia) and drug-induced effects on function. Thrombocytopenia can arise from three mechanisms:

1) failure of platelet production (e.g. aplastic anaemia, leukaemia, vitamin B12/folate deficiency)

2) shortened platelet half life (e.g. auto-immune thrombocytopenia, thrombotic thrombocytopenia, infections, drugs) and

3) increased pooling of platelets in an enlarged spleen.



There are three laboratory tests to monitor platelets, the platelet count, the bleeding time and platelet aggregation. The most important of these is the platelet count, as progressive reduction of platelets dramatically increases the risk of bleeding. Platelet aggregation is performed to monitor platelet dysfunction and can be used to measure von Willebrand factor activity. The bleeding time is now rarely used in clinical practice although it is sometimes required if it is necessary to assess vessel wall function.

The blood coagulation system is portrayed as an enzymatic cascade by which trace initiators generate large amounts of thrombin to clot fibrinogen and aggregate platelets. Traditionally, the cascade is described in terms of the intrinsic, extrinsic and common pathways.





This description is still useful for understanding the use of laboratory tests. However, it is important to realise that in vivo the intrinsic pathway (initiated by factor XII activation) plays a minimal role in normal haemostasis. The main initiator is thought to be tissue factor, exposed by vessel damage, which forms an activation complex with factor VIIa. Tissue factor/ factor VIIa also activates the intrinsic pathway at the level of factor IX. Certain of the clotting factors (factors VII, IX, X and prothrombin) bind to phospholipid in order to activate their substrate factor. Phospholipid binding requires Vitamin K dependent post translational modification of certain amino acids (“Gla” residues) and is mediated by Ca2+ ions.

Factors VIII and V, once activated, accelerate these membrane-dependent reactions on the platelet surface, enabling clotting to be localised to the sites of vessel injury.

Anticoagulant control of blood coagulation is achieved with the drugs heparin (which accelerates the inhibition of thrombin and other clotting proteinases by antithrombin) and warfarin (which inhibits the post translational Gla modifications of certain of the clotting proteinases, thus reducing their activities).

The main tests of coagulation function are the activated partial thromboplastin time (APTT) and the prothrombin time (PT). The APTT monitors the function of the intrinsic and common pathways and is used to control the level of heparin in patients. The PT monitors the extrinsic and common pathways and is used to control levels of oral anticoagulant (warfarin) in patients. These tests are also used to detect inherited coagulation abnormalities such as haemophilia A and B (factor VIII or factor IX deficiency: APTT used) and acquired disorders such as disseminated intravascular coagulation (both tests).

Fibrinolysis is initiated by fibrin clot formation. This facilitates the activity of the main plasminogen activator, tissue plasminogen activator (tPA). tPA activates plasminogen to plasmin, which lyses the fibrin clot in a specific reaction.

In broad terms, bleeding due to platelet-vWF and coagulation defects can be distinguished clinically.   
The former are characterised by superficial bleeding into the skin and mucosal membranes and by bleeding immediately following injury. Bleeding from coagulation factor deficiencies tends to be into deep tissues, muscles and joints. It is often delayed after injury but is prolonged and can be severe. The haemophilias are well known sex linked recessive disorders of this latter type. Von Willebrand disease is another inherited disorder. Its inheritance is usually autosomal dominant. Bleeding in this disorder may be of characteristically vascular (e.g. nosebleeds, menorrhagia and prolonged bleeding from superficial cuts) due to its importance in the platelet-vessel wall interaction, but because this factor is a carrier for factor VIII, it can also resemble the haemophilias.

Treatment of bleeding arising from acquired platelet and coagulation factor abnormalities requires identification and treatment of the underlying conditions. If it cannot be corrected then replacement therapy may be possible. Inherited deficiencies (e.g. haemophilia, von Willebrand disease) tend to be treated by replacement therapy. Drugs are available to inhibit (tranexamic acid) or enhance (tPA) fibrinolysis.