

# HAEMATOLOGY PHYSIOLOGY 2

**Hemostasis** is the process of blood clot formation at the site of vessel injury. When a blood vessel wall is disrupted, the hemostatic response must be quick, localized, and carefully regulated. Although the clotting process is a dynamic, **highly interwoven** array of **multiple processes**, it can be viewed as occurring in **four phases**, which are discussed in detail in the following sections:

## 1. Initiation and formation of the platelet plug

The functional response of activated platelets involves four different processes:

- \* **Adhesion** — the deposition of platelets on the subendothelial matrix
- \* **Aggregation** — platelet-platelet cohesion
- \* **Secretion** — the release of platelet granule proteins
- \* **Procoagulant activity** — the enhancement of thrombin generation

## 2. Propagation of the clotting process by the coagulation cascade

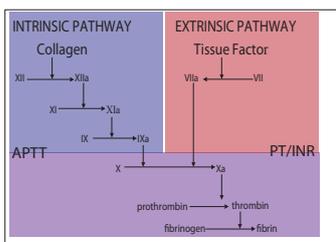
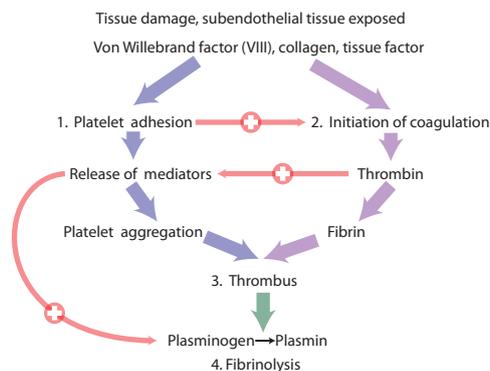
Is described classically by the **intrinsic** and **extrinsic pathways**. This describes *in vitro* but probably not *in vivo*. It is useful to **explain coagulation testing**. Is described currently by in terms of three phases; **initiation**, **amplification** and **propagation**. See below for details.

## 3. Termination of clotting by antithrombotic control mechanisms

Coagulation is modulated by a number of mechanisms: **dilution of procoagulants** in flowing blood, **removal of activated factors** through the reticuloendothelial system, especially in the liver, and control of the activated procoagulants and platelets by **natural antithrombotic pathways**. These antithrombotic pathways are all anchored on vascular endothelial cells, which play an active role in maintaining the fluidity of blood. The termination phase of the coagulation process involves **two circulating enzyme inhibitors**, **antithrombin** (formerly called antithrombin III) and **tissue factor pathway inhibitor** and a **clotting-initiated inhibitory process**, the **protein C pathway**. In addition, **prostacyclin**, **thromboxane**, and **nitric oxide** modulate vascular and **platelet reactivity**.

## 4. Removal of the clot by fibrinolysis

To restore vessel patency following hemostasis, the clot must be organized and removed by the proteolytic enzyme plasmin in conjunction with wound healing and tissue remodeling. **Plasminogen**, the precursor molecule to plasmin, **binds fibrin** and **tissue plasminogen activator (tPA)**. This ternary complex leads to **conversion** of the proenzyme plasminogen to active, **proteolytic plasmin**. While tPA is largely responsible for initiating intravascular fibrinolysis, urokinase (extravascular) and streptokinase can also activate plasminogen to plasmin.



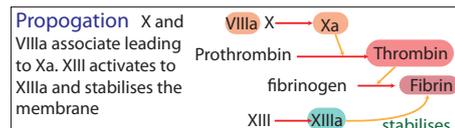
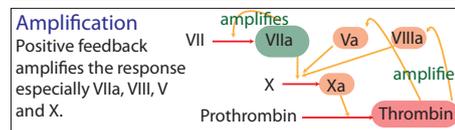
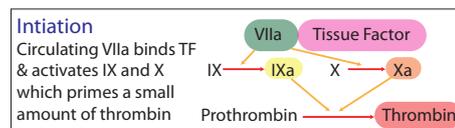
The **coagulation cascade** is traditionally conceived in terms of the **intrinsic** and **extrinsic pathways**. Whilst this is a **useful** method for describing what happens **in vitro** (and therefore clotting tests such as **APTT** and the **PT/INR**) it **does not adequately describe** what happens **in vivo**. A unified method of describing the coagulation process is in three major phases; initiation, amplification and propagation.

**Initiation:** clotting is initiated through a sequence of events **broadly analogous to the extrinsic pathway**. **Tissue factor**, which is not found in the circulation but is found in the subendothelium and other surfaces **reacts with circulating coagulation proteins**, in particular **VII**, which is activated to **VIIa** and then **activates small quantities of X and IX to Xa and IXa** respectively.

These basically 'prime' as **small amount of prothrombin (II) to thrombin (IIa)**. The thrombin activates platelets and encourages coagulation factor attachment.

**Amplification:** Is characterised by **positive feedback mechanisms** which ramp up the process, in particular by increasing **VIIa** production, by activating **VIII** and **V** to increase prothrombin activation to thrombin, and enhancement of **Xa** and **IXa** production.

**Propagation:** During propagation **large amounts of X** associate with **VIIIa** on the surface of platelets, activating **X** to **Xa** and further **increasing thrombin formation** and therefore fibrin formation. Stabilisation of the the fibrin clot then occurs via **activation of XIII to XIIIa** which **crosslinks the fibrin monomers into a stable fibrin matrix**.



**Physiological mechanisms for preventing thrombosis.** Endothelium absorbs mediators involved in inflammatory response and coagulation:  $PGF_2$ , serotonin, adenosine, histamine, complement and other mediators. It synthesizes or releases **plasminogen activator**, **proteoglycan**,  $PGI_2$ , **heparin** and **protein C** which play an **inhibitory role in coagulation** as well as factor VIII, von Willebrand factor and tissue factor. **Antithrombin** is synthesized in the liver and circulates in the plasma. Because normal blood coagulation is a positive-feedback process, there are mechanisms to prevent inappropriate spontaneous coagulation and limit the spread of clot. The **endothelium is smooth and lined with glycocalyx** which repels platelets and clotting factors. **Thrombomodulin** is bound to the endothelial membrane. It binds thrombin and, when thrombin is bound, **activates protein C and protein S** which **inactivate factors V and VIII**. The release of  $PGI_2$  from the endothelium **inhibits thrombus formation**. It acts via intracellular cAMP on endothelial smooth muscle to produce vasodilation and platelets to inhibit aggregation and the production of phospholipid. In the process of clot formation, thrombin is strongly bound to fibrin fibres, limiting its range of action. The plasma protein antithrombin binds circulating thrombin and inactivates it. The action of antithrombin is greatly enhanced by binding of antithrombin III to heparin. Heparin-antithrombin complex also binds activated factors XII, XI, IX and X. Small amounts of **heparin** are released from **mast cells and basophils** and this presumably plays a role in the lysis of small pulmonary emboli, but systemic anticoagulation is rapidly induced using large IV doses of heparin derived from animal tissues. Heparin is a collection of polysaccharides of different molecular weights, all of which are highly negatively charged. Fractions of the range of heparin molecules are used clinically. The effect of heparin can be titrated using protamine, a highly positively charged molecule which binds circulating heparin and prevents it from acting as an anticoagulant. **Alpha<sub>2</sub>-macroglobulin** is a plasma protein which binds activated clotting factors but does not inactivate them.

**Physiological consequences of acute and chronic anaemia.** Anaemia is defined as a **reduction in red cell mass below the normal range**. The normal range differs with age, sex, environment and pregnancy. **Acute blood loss**, as in surgery, results in rapid **fluid shift** from the interstitial compartment to the intravascular compartment, usually supplemented by IV fluid. This results in a rapid **fall in red cell count due to dilution**. The immediate effects of an acute fall in red cell mass are a reduction in the **viscosity of blood** and a reduction in the **oxygen carrying capacity** of blood. Oxygen carrying capacity =  $[Hb] \times SaO_2 \times 1.34 + \text{Dissolved O}_2$ , (recall that delivery is this figure times cardiac output), so a fall in Hb from 150 g/l to 100 g/l results in a fall in oxygen carrying capacity from 20 ml/100 ml to 14 ml/100 ml. If metabolic rate is unchanged, this requires a **lower mixed venous PO<sub>2</sub>** or **increased cardiac output** to maintain oxygen flux. Both of these changes occur, the rise in CO being facilitated by the reduction in viscosity. Impaired tissue oxygenation also results in **increased production of 2,3DPG** which facilitates oxygen transfer by moving the **dissociation curve to the right**. Dyspnoea results in **increased ventilation** with some increase in PAO<sub>2</sub>. Within hours of acute blood loss, **red cell production rises**, stimulated by the impairment of tissue oxygenation causing **release of erythropoietin**. A **rise in reticulocyte count to 10-15% over a week** and a rise in platelet and white cell counts occur as they are mobilized from marginal sites. The physiological changes in **chronic anaemia** depend partly on the cause of the anaemia. Reduction in oxygen carrying capacity is always present and results in the **same physiological responses** as acute anaemia: increased ventilation, CO, 2,3DPG and reduced mixed venous PO<sub>2</sub>. The **haematological changes depend on the cause of the anaemia** which can be classified as haemorrhagic, aplastic or haemolytic and subclassified in more detail.