Chapter 19

OVERVIEW OF A COMPLICATED SYSTEM: THE COAGULATION SYSTEM

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The concept of blood coagulation dates back to 1960's when Davie, Ratnoff and Macfarlane described the "waterfall" and "cascade" theories outlining the fundamental principle of cascade of proenzymes leading to activation of downstream enzymes (1). Haemostasis, defined as arrest of bleeding, comes from Greek, haeme meaning blood and stasis meaning to stop (2).This thrombohaemmorhagic balance is maintained in the body by complicated interactions between coagulation and the fibrinolytic system as well as platelets and vessel wall.

Blood coagulation and platelet-dependent primary hemostasis have evolved as important defence mechanisms against bleeding. The activation of coagulation is temporally co-ordinated with the primary platelet plug formation. The coagulation system is carefully controlled by several anticoagulant mechanisms, which under normal conditions prevail over the procoagulant forces. Disturbances of the natural balance between the pro- and anticoagulant systems caused by genetic or aquired factors mayresult in bleeding or thrombotic diseases.

PRIMARY HAEMOSTASIS

Vascular wall damage exposes blood to subendothelial tissues, which triggers the primary haemostasis events. Coordinated interactions between platelet receptors, plasma proteins, and tissue components seal the wounded area. A series of reactions including platelet adhesion, aggregation, release of granule content, and morphological changes generate the platelet plug. The von Willebrand factor (VWF), a high molecular weight plasma protein composed of multiple disulphidelinked subunits is important for the initial adhesion of platelets. Newly produced VWF multimers can be >20 million Da in mass and 4 um in length. In plasma, they undergo proteolytic processing by the metalloprotease ADAMTS 13.

Platelets are disc shaped, anucleate cellular fragments derived from megakaryocytes. They have a pivotal role in haemostasis by forming the initial hae-

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As with the coagulation system, the fibrinolytic system has components that are age-dependent (24) . The capacity to generate and inhibit plasmin during infancy and throughout childhood is very similar to adults (24) . There are significant differences in the levels of the fibrinolytic components between children and adults. Some fibrinolytic components are lower at birth when compared to adults, especially plasminogen (75% and 50% of adult values for the healthy premature and full-term newborns, respectively) and the primary inhibitor of plasmin, α 2 AP (at 80% of adult values) (24) . However, the levels of fibrinolytic activators such as tPA and uPA and regulators such as PAI-1 are elevated at birth compared with adults (24,25,26).Although α 2 M has a major role in the inhibition of thrombin in coagulation during infancy and childhood, the importance of α 2 M in plasmin inhibition in the fibrinolytic system in the young is unclear (24) .

TAFI is a plasma zymogen that can be activated by thrombin, the thrombin–TM complex, or plasmin (23,24) . The activated form of TAFI removes C-terminal lysine residues of plasminmodified fibrin that mediates a positive feedback mechanism in plasminogen activation, thereby attenuating fi brinolysis (23,24,27). The TAFI pathway is active in vivo and most likely provides the proper balance between fibrin deposition and fibrin degradation.

Hemostasis involves the stoppage of bleeding following an injury to the vasculature. The various systems work together to maintain the integrity of this process and prevent what would otherwise be a traumatic reaction. A delicate balance is maintained between all of the systems that are involved in the hemostatic process. For centuries, there have been conceited efforts to understand the coagulation process and design accurate methods for evaluation and monitoring of this complex process. It is hoped that the clinical laboratory will continue to be at the forefront in the elucidation of the intricate processes that constitute hemostasis.

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