ANIMAL MODELS IN HEMOSTASIS AND THROMBOSIS

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INTRODUCTION

The hemostatic mechanism comprises a complexity of interactions between components in the intravascular compartment, such as elements contained in the mechanisms of blood coagulation, blood platelets, and the vessel wall. Essential to life is the balance of activities in the homeostatic state; otherwise, blood would be a gel rather than a fluid. The former would not be compatible with life, which depends on the fluid state of blood except in injury to the blood itself or the vessel wall (1), resulting in a hemostatic plug or a thrombus.

Thrombus formation involves interaction of constituents in the vessel wall, activation of the blood coagulation mechanism, platelet aggregation and release of thrombogenic activators. Thrombi can result in serious clinical problems and even death for man and animals. Conversely, without the formation of a hemostatic plug involving the same constituents and mechanisms, life can be endangered, as the hemophilic human or animal exemplifies (2-10).

Hemostasis involves clotting factors in the extrinsic system or tissue pathway and the intrinsic compartment pathway. Primary hemostasis consists of a series of reactions following vascular trauma. Hemostasis involves release of tissue thromboplastins, as well as activation of Factor VII and Factor X, platelet activation - release of Platelet Factor 3 (PF3), activation of von Willebrand's Factor (VWF), adhesion of platelets to subendothelial elements (collagen), resulting in release of platelet constituents, adenosine diphosphate (ADP) lipozymes, phospholipids, etc., resulting in aggregation of additional platelets (11-13). Activation of coagulation factors, conversion of prothrombin to thrombin and fibrinogen to fibrin, polymerization of fibrin, activation of Factor XIII (fibrin-stabilizing factor), associated with release of vasoconstrictor substances (epinephrine) enhancing vascular response, coupled to the formation of the platelet or hemostatic plugs, effectively produces cessation of bleeding and a stable hemostatic plug.

The requirements of "adequate veterinary care" and management are essential in the utilization of spontaneous, hereditary or acquired animal models of hemorrhagic disease, or those experimentally induced. Bleeding animals can suffer significant pain and distress. Therefore, the study of these diseases requires the investigator and all of those responsible for the care and handling of these animals to be guided by sensitivity and humane and ethical considerations, as well as an understanding of the hemostatic mechanism.

The prevention of pain and distress can best be handled by keeping the animal quiet and isolated from noise and extraneous, arousing stimuli. In most cases, the use of analgesics and tranquilizers is contra-
indicated because of their effect on the reactivity of blood platelets, the aggregation and release mechanism, an essential in hemostasis.

The provision of "tender loving care" is the best treatment to assure the comfort of the animal and a return to a homeostatic balance. The provision of fresh active deficient factors, i.e. normal plasma, or platelet rich plasma, are essential for hemostasis.

HEMOPHILIA

Congenital diseases such as hemophilia are expressed in the same manner in animals as in humans (8, 14, 15).

Although it was obvious that in hemophilia an injury to the vessel wall resulted in the formation of a poor or inadequate hemostatic plug, it was not until the late 1970's that the mechanisms were revealed (8, 16, 17).

In the vessel wall, especially in the endothelium, prostaglandins are synthesized from arachidonic acid derived from phospholipid metabolism. The major end product at the site of the vessel wall is the production of prostaglandin I₂ (prostacyclin), an inhibitor of platelet aggregation and a potent vasodilator. When vascular injury occurs, platelet stimulation results. Arachidonic acid from the platelet membrane, following the same pathway as prostacyclin, is acted upon by thromboxane synthetase from the injured aggregating platelets to form Thromboxane A₂ in circulating blood platelets (11, 18, 19, 20), this accelerates platelet aggregation and release.

Recently, research has further elucidated mechanisms which explain the maintenance of the fluid state of blood although the hemostatic mechanism may be activated. Thrombomodulin (T.M.) is a cell surface protein found on endothelial cells that binds thrombin and increases its ability to activate protein C, a serine protease zymogen. Activated protein C becomes a potent anticoagulant, selectively inactivating Factors V and VIII, as well as modulating the fibrinolytic system (21).

ANIMAL MODELS IN THE STUDY OF HEMOSTASIS

The importance to research in finding an animal model is how accurately that model resembles the disease state in human subjects. As well, a model may prove useful if it provides new insights, or allows the examination of single or multiple factors involved in the production of disease (22, 23).

The search for animal models for bleeding disorders such as hemophilia has been spurred on by the needs and demands of hemophilic patients. Such individuals long for the day when the researcher will develop an agent which, when injected, (perhaps not necessarily into a vein), would prevent all bleeding and its associated pain.

Giles (24) has demonstrated the value of a dog with naturally-occurring hemophilia, reporting on the genetic engineering of Factor VIII (Hemophilia A) which could in future lessen the risk of serious problems such as impurities and blood-borne viral contamination from diseases such as hepatitis and Acquired Immunity Deficiency Syndrome (AIDS).

Giles, Mann and Nesheim (25) have developed a bypass product, Factor Eight Bypassing Activity (FEBA), for the 10-15% of hemophiliacs who form antibodies against Factor VIII and thus prevent replacement Factor VIII from forming a stable hemostatic plug. This bypass product (FEBA) consists of small amounts of Factor X combined with coagulant active phospholipids.