HEMOSTASIS

DEFINITION: Hemostasis is the cessation of bleeding following interruption of vascular integrity. It involves the blood vessels, platelets, plasma proteins, blood coagulation, and dissolution of clots. In normal hemostasis, a "steady state" exists between the formation and dissolution of thrombi.

FOUR PHASES:
1) Constriction of damaged vessels to restrict blood flow to injured tissues
2) Formation of temporary platelet plug
3) Formation of a fibrin mesh or "clot" around the "plug" of platelets and RBC
4) Partial or complete dissolution of the clot by plasmin

TYPES OF CLOTS:
1) White thrombi contain fibrin, platelets, and very few RBC; they are found in injured or abnormal blood vessels, especially the arteries.
2) Red thrombi contain fibrin, RBC, and some platelets; they are found at sites of injury. This is the type of thrombus that begins with a platelet plug, and what we usually refer to as "clots."
3) Fibrin deposits contain fibrin only, and are found in small vessels and capillaries.

FORMATION OF FIBRIN: Fibrin is formed from fibrinogen at the terminal end of the blood clotting cascade. Consult your textbook and/or other references for a review of this cascade. The cascade is triggered in two ways:

1) The "Intrinsic Pathway" commences with the "contact phase." When certain blood clotting factors are exposed to a rough, negatively charged surface, they in turn set off the cascade of zymogen activations eventually resulting in the activation of Factor X. This rough, negatively charged surface is usually collagen exposed on the surface of a blood vessel.
2) The "Extrinsic Pathway" commences when injured tissues release a substance known as "tissue factor," which acts as a cofactor in the activation of Factor X by Factor VII.

The activation of Factor X commences the "Final Common Pathway." Activated Factor X cleaves prothrombin (Factor II), forming active thrombin on the surfaces of activated platelets. Thrombin in turn cleaves fibrinogen (Factor I), forming fibrin.

WHERE AND WHAT IS FIBRINOGEN? Fibrinogen is a soluble plasma glycoprotein, MW = 340,000, which is primarily synthesized in the liver. Cleavage of fibrinogen by thrombin removes only two percent of the protein, but exposes binding sites which allow fibrin to aggregate. Note that thrombin also activates Factor XIII, which acts to covalently crosslink fibrin molecules, forming a more stable clot.

ANTICOAGULANTS: Within the body, the concentrations of free circulating thrombin must be controlled, or disastrous clots would form throughout the body. Four different proteins exist in normal plasma which are inhibitors of thrombin. The most important of these is antithrombin III.
1) Antithrombin III not only inhibits thrombin, but binds to and inhibits several other clotting factors.
2) Heparin, an acidic proteoglycan, binds to antithrombin III and greatly potentiates its activity. (This is the clinical basis for heparin use as an anticoagulant.)
3) The "coumarin drugs" (such as Dicoumarol, Warfarin) act in a different fashion, inhibiting the vitamin-K dependent formation of several clotting factors.

DISSOLUTION OF FIBRIN CLOTS: Both fibrin and fibrinogen are degraded by a serine protease called plasmin. Plasmin, like the clotting factors, is also an activated zymogen:
1) Plasminogen is the zymogen precursor of plasmin, and is freely circulating in the plasma. If soluble plasminogen is converted to soluble plasmin in the serum, it is quickly inactivated by alpha2-antiplasmin.
2) Plasminogen has high affinity for both fibrin and fibrinogen, so it becomes incorporated into clots as they form. Clot-bound plasminogen converted to clot-bound plasmin in protected from inhibition by alpha2-antiplasmin, so the plasmin remains active here.
3) **Tissue Plasminogen Activator** is another serine protease, which activates plasminogen to form plasmin. It is released from the vascular endothelium under condition of injury or stress.

4) Tissue Plasminogen Activator (TPA) is inactive unless it is bound to fibrin. Once TPA binds to fibrin, TPA will cleave plasminogen in the clot to form plasmin. The activated plasmin then dissolves the clot by degrading the fibrin in the clot.

5) **Urokinase** is a second activator of plasminogen which does not have affinity or selectivity for fibrin. When present in the blood, it will tend to form plasmin from plasminogen in the serum, and not isolate this activation to actual clots, as does TPA. The natural function of urokinase is to clear away any fibrin which may have been deposited in the renal tubules.

THE ROLE OF PROSTACYCLINS IN HEMOSTASIS: Endothelial cells in the walls of blood vessels synthesize prostacyclins, which inhibit platelet aggregation. (Prostacyclins oppose the activity of the thromboxanes, which stimulate platelet aggregation).

1) Both the prostacyclins and thromboxanes are eicosanoid hormones.

2) Prostacyclins, when binding their receptors on platelet membranes, apparently activate adenylate cyclase inside of the platelets, forming cAMP from ATP, and causing their effects.

3) Thromboxanes, when binding their receptors on platelet membranes, apparently activate phospholipase C inside of the platelets, forming DAG and IP3 from phosphatidylinositol bisphosphate, causing their effects.