WHY DO HEMOPHILIACS BLEED?

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Deficiency of coagulation factor VIII (antihemophilic factor) and coagulation factor IX (Christmas factor) result in Hemophilia A and Hemophilia B, respectively. Patients with severe deficiency experience frequent spontaneous bleeding, most commonly hemarthrosis in large joints. Bleeding associated with trauma or surgery is life threatening unless properly treated. The severity of the clinical manifestations is directly related to the degree of factor deficiency(l). But intriguingly enough, factors VIII or IX are not involved in the extrinsic pathway of coagulation, where tissue factor plays the predominant role in initiation of hemostasis. Then the question arises, why do hemophiliacs bleed? The simplistic answer that they are deficient in factor VIII or IX is not satisfactory, since hemostasis should be achieved via the extrinsic pathway which is intact in these patients and does not involve factor VIII or IX. This review offers to resolve this dilemma by pointing towards recent research which has led to the proposal of a revised hypothesis of blood coagulation.

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Coagulation Physiology-The Cascade Waterfall Hypothesis

When a blood vessel wall is ruptured, platelets adhere to the exposed subendothelium and become activated, beginning the process of aggregation. The platelet plug thus formed provides a surface on which certain coagulation factors can become activated and initiate the coagulation cascade(2). The coagulation cascade is the serial activation of coagulant factor zymogens to their active enzymatic forms until thrombin converts fibrinogen to fibrin *(Fig. 1)*. Fibrin monomers rapidly polymerize to fibrin strands, and the resultant clot is further stabilized by the cross-linking action of factor XIII. The coagulation cascade can be initiated and proceed along either the extrinsic pathway or the intrinsic pathway(3). The two pathways converge at the activation of factor X, and the final sequence of events is the same for both. The clotting cascade is seen as a biological amplifier; the gain of this amplifier system is modulated by several negative and positive feedback loops. Several interactions occur at various levels of the two systems.

Intrinsic Pathway

Factor XII (F XII) circulates in the blood as an inactive zymogen. The con-

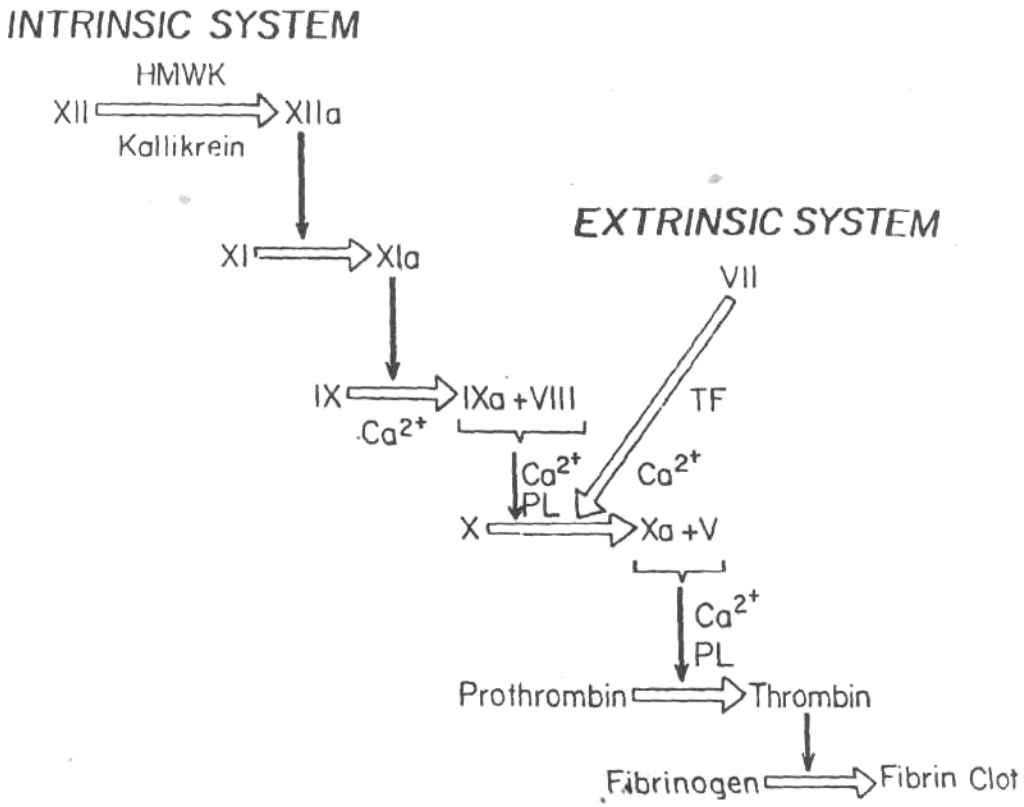

Fig. 1. Coagulation cascade: Intrinsic and extrinsic pathway.

tact system is initiated when F XII binds to a negatively charged surface *(e.g.,* damaged endothelium), and converts it by autoactivation of F Xlla. Surface bound F XIIa activates prekallikrein to kallikrein, which further activates F XII. This reaction is enhanced by high mo lecular weight kininogen (HMWK). HMWK also acts as a cofactor for the activation of F XI by F Xlla. F XIa then activates FIX in a calcium dependent reaction. Calcium ions act as bridges binding FIX molecule to phospholipid. F X is next activated to F Xa by a reaction which takes place on the cell surface and involves a complex of F IXa, thrombin-activated F VIIIc, calcium ions and phospholipid(4).

Extrinsic Pathway

The active component of tissue factor (TF) released from damaged cells is a lipoprotein complex, which acts as a cell surface receptor for F VII, activating it to F Vila in the presence of calcium ions. Factor X then binds to the complex and becomes activated(5).

Common Pathway

F Xa, formed by either the intrinsic or extrinsic pathway, forms a cell surface complex (the prothrombinase complex) with phospholipid, calcium ions and thrombin activated F Va. This complex cleaves prothrombin (II) into thrombin (FIIa). Thrombin converts fibrinogen (FI) to fibrin monomers and also activates FXIII. Fibrin monomers rapidly polymerize forming an insoluble fibrin gel. F XHIa acts as a transaminase in the presence of calcium ions, forming covalent bonds between fibrin polymers, thus stabilizing the fibrin clot(6).

Revised Hypothesis of Blood Coagulation

The generation of thrombin is the first major step in normal hemostasis. It is now apparent, that *in vivo,* for the generation of adequate amounts of thrombin, interactions between the above mentioned pathways is essential. It has been suggested that, *in vivo,* there is only one pathway of coagulation and different mechanisms of activation(7). The revised hypothesis of coagulation postulates a single pathway(8). Coagulation ensues when damage to blood vessels allows the exposure of blood to the tissue factor produced constitutively by cells beneath the endothelium. The F VII or F Vila present in plasma then binds to tissue factor and the F VIIa/TF complex activates limited quantities of factor X and factor IX(9).

With the generation of F Xa, the inhibitory effect of tissue factor pathway inhibitor (TFPI) becomes manifest, preventing further production of F Xa and F IXa by F VIIa/TF(10). Additional F Xa can be produced only through the alternative pathway involving F IXa and F Vllla(ll). Thus only the action of F IXa and F Villa can generate the additional F Xa needed to sustain coagulation. In this regard, F XI activation by thrombin and F XIa autoactivation may generate additional F IXa *(Fig. 2).* The revised hypothesis of blood coagulation differs from the cascade-waterfall model in various respects. Factor XI rather than being involved in the initiation of coagulation, is activated late in the coagulation process, after F Xa and thrombin have been generated through the action of F VIIa/TF(12). Most significantly it integrates all of the factors known to be involved in coagulation into a single pathway that is initiated by F VIIa/TF and that does not require the contact factors (F XII, PK, HMWK). Besides, in the revised model, the hemostatic process does not end with the initial generation of F Xa and thrombin. Instead, the initial hemostatic response must be consolidated by the progressive local generation of F Xa and thrombin for normal hemostasis has been shown *in vivo(13).*

Why do Hemophiliacs Bleed?

In normal hemostasis, F VIIa/TF is responsible for initial F Xa generation, which provides sufficient thrombin to induce the local aggregation of platelets and the activation of the critical cofactors, F V and F VIII. Persistent hemostasis requires the continued production of additional F Xa through the action of F IXa and F Villa, since the F Xa generation by F VIIa/TF is inhibited by TFPI(14). TFPI-induced feedback inhibition of F VIIa/TF explains the clinical need for both the extrinsic and intrinsic (F VIII, IX, XI) coagulation pathways for normal hemostasis(15). Thus,

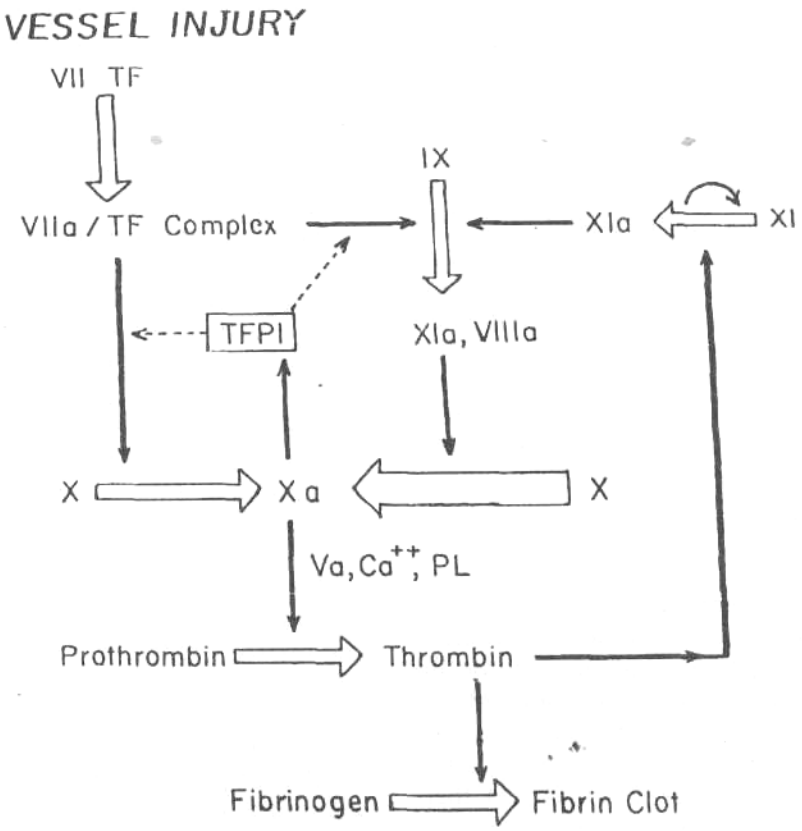

fig. *2. Revised tissue factor pathway of coagulation.*

hemophilia patients bleed because the F Xa generated through the action of F VIIa/TF, and dampened by TFPI, is insufficient to sustain hemostasis and must be amplified through the action of F IXa and F VIIIa(16). And that persistent hemostasis requires the continued production of F Xa through the action of F IXa and F VlIIa is consistent with the delayed onset of bleeding frequently seen in hemophilia(17). As a corollary it has been suggested that effective inhibition of TFPI could ameliorate the hemorrhagic manifestations of hemophilia(18).

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