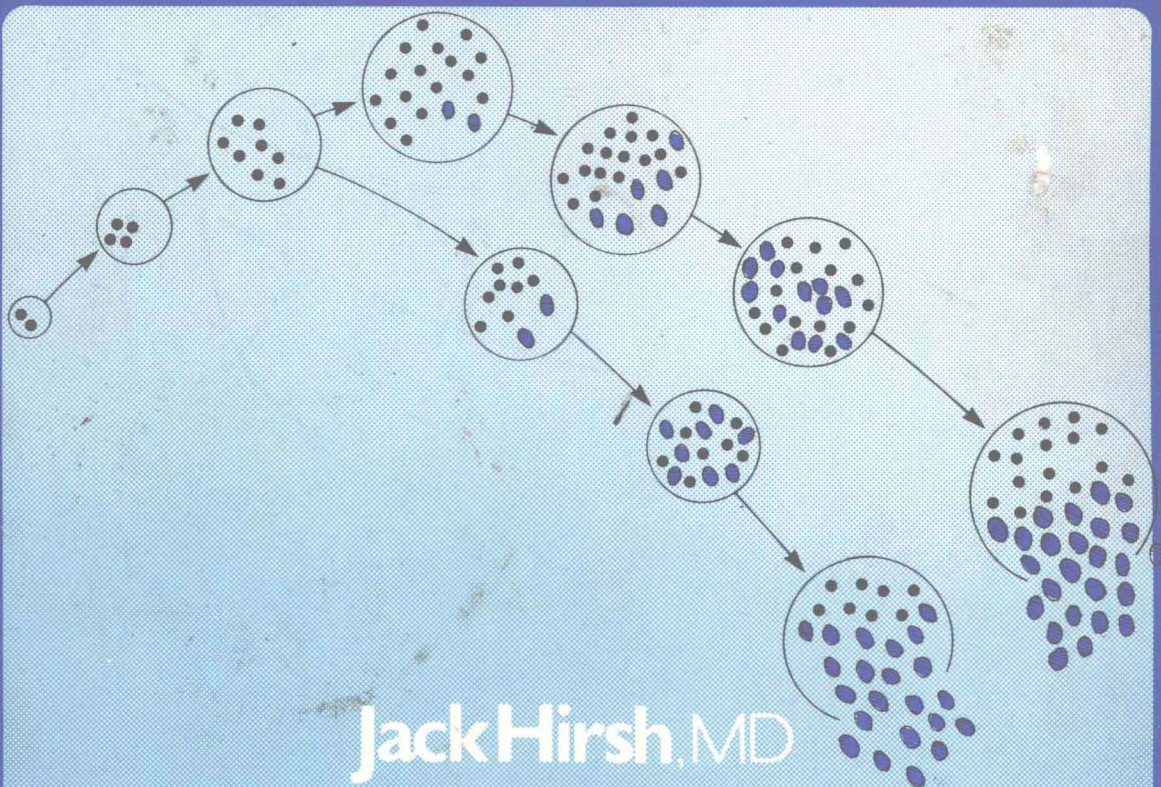


HEMOSTASIS & THROMBOSIS

A CONCEPTUAL APPROACH

Second Edition



Jack Hirsh, MD
Elizabeth A. Brain, MD



Churchill Livingstone

HEMOSTASIS (& THROMBOSIS

A CONCEPTUAL APPROACH

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SECOND EDITION

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Produced through the facilities of
McMaster University Audiovisual Services

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Churchill Livingstone New York, Edinburgh, London, and Melbourne 1983

Second Edition
© Churchill Livingstone Inc. 1983
First Edition © Longman Inc. 1979
First revision published by Churchill Livingstone 1979
First published by McMaster University 1976

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Distributed in the United Kingdom by Churchill Livingstone, Robert Stevenson House, 1-3 Baxter's Place, Leith Walk, Edinburgh EH1 3AF and by associated companies, branches and representatives throughout the world.

ISBN 0-443-08220-0

Printed in USA

7 6 5 4 3 2

Library of Congress Cataloging in Publication Data

Hirsh, Jack, 1935 -
Hemostasis & thrombosis.

Bibliography: p.

1. Blood -- Coagulation, Disorders of.
2. Hemostasis. 3. Thromboembolism. 4. Hemorrhagic diseases. I. Brain, Elizabeth A., 1933 -
II. Skov, Knud C. III. Pulver, Molly. IV. Hirsh, Anna.
V. Title. VI. Title: Hemostasis and thrombosis.

[DNLM: 1. Hemostasis. 2. Thrombosis.

WH 310 H489h]

RC647.C55H57 1983 616.1'57 82-19726

ISBN 0-443-08220-0

Preface

to the Second Edition

A number of important advances have been made in the field of hemostasis and thrombosis since the first edition was published six years ago. The more notable of these have been incorporated in the second edition which has also been expanded by including new chapters on thrombosis. The section on hemostasis now includes a more comprehensive discussion of abnormalities of the Factor VIII molecule in hemophilia and von Willebrand's disease, of the interaction between the platelet surface and blood coagulation factors, of recent advances in the understanding of fibrinolysis, and a discussion of the abnormalities of platelet membrane glycoproteins responsible for defects in platelet adhesion and platelet aggregation.

The chapter on pathogenesis of thrombosis has been expanded and three new chapters have been added to bring the reader up-to-date on the epidemiology, clinico-pathological correlations and manifestations of venous, arterial and intracardiac thrombosis and on the principles of diagnosing thromboembolism. The section on treatment of thrombosis has been expanded to incorporate some of the recent advances in prophylaxis and to include a discussion of the molecular basis for the mode of action of antithrombotic agents. As in the first edition, each chapter ends with self-assessment questions which have been updated to reflect the changes in the new edition.

May 1982

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1 An Introduction to Normal Hemostatic Mechanisms	1	7 Inherited Coagulation Disorders	66
Normal hemostatic mechanisms, including vessel constriction, platelet adhesion to collagen, platelet release and aggregation with ADP, blood coagulation and consolidation of the platelet plug by fibrin, and subsequent fibrinolysis.		Control of synthesis of the Factor VIII molecule. Hemophilia and Christmas disease, inherited as sex-linked recessive traits and von Willebrand's disease, inherited as an autosomal dominant trait. Details of the very rarely encountered autosomal recessive traits are not included.	
2 An Introduction to Abnormal Hemostatic Mechanisms	20	8 Acquired Coagulation Disorders	79
Bleeding disorders due to defects of blood vessels, platelets, coagulation factors and excessive fibrinolytic activity. Thrombosis due to inappropriate activation of coagulation or failure of protective mechanisms. Consequences and complications of thrombosis.		Common acquired coagulation disorders, including vitamin K deficiency, liver disease, massive transfusion syndrome and consumption coagulopathy due to diffuse intravascular thrombosis.	
3 Clinical Diagnosis of Bleeding Disorders	30	9 Pathogenesis of Thrombosis	92
Clinical manifestations of bleeding disorders. Importance of history-taking including family history and response to previous surgery or trauma. Difference between platelet, vascular, and coagulation disorders. Patterns of inheritance.		Pathological characteristics of thrombi forming in high and low flow systems and the fate of thrombi. Thrombosis as a result of imbalance between thrombogenic factors and protective mechanisms. The role of these different factors in veins, arteries and the heart.	
4 Laboratory Diagnosis of Bleeding Disorders	39	10 Manifestations of Venous Thrombosis and its Sequelae	110
Principles and significance of laboratory diagnosis of bleeding disorders. Screenings tests for platelet and vascular disorders (i.e. tourniquet test, bleeding time and platelet count) and coagulation disorders (i.e. thrombin time, prothrombin time and partial thromboplastin time). Special tests mentioned briefly.		Signs of leg vein thrombosis. Pulmonary embolus as the major complication of leg vein thrombosis, and its effects on respiratory and cardiac function. Post-phlebitic syndrome.	
5 Vascular Disorders	47	11 Clinical Manifestations of Arterial & Intracardiac Thrombosis and their Sequelae	122
Characteristic features of easy skin and mucous membrane bleeding. Hereditary telangiectasia and acquired vascular disorders of simple bruising, senile purpura, Henoch Schönlein purpura, and purpuras due to drugs, infection, scurvy, Cushing's disease and excessive corticosteroid administration.		Role of hypertension and atheroma. Symptoms of peripheral, visceral and coronary artery occlusion. Stroke and transient ischemic attacks.	
6 Platelet Disorders	54	12 Diagnosis of Thrombosis	132
Bleeding disorders due to numerical or functional abnormalities of the platelets. Their normal derivation from precursor stem cells through polyploid megakaryocytes and fate in the circulation and spleen. Abnormalities due to impaired production, decreased survival or increased splenic pooling. Platelet function disorders due to abnormalities of adhesion, release of ADP, aggregation, or platelet coagulant activity.		Venography, impedance plethysmography, ¹²⁵ I-Fibrinogen Leg Scanning, Angiography, Doppler Ultrasound and Lung Scanning.	
		13 Prevention and Treatment of Thrombosis	143
		Mode of action of the three classes of drugs used in the treatment of thrombosis: the anticoagulants (heparin and vitamin K antagonists) antiplatelet drugs, and fibrinolytic agents.	

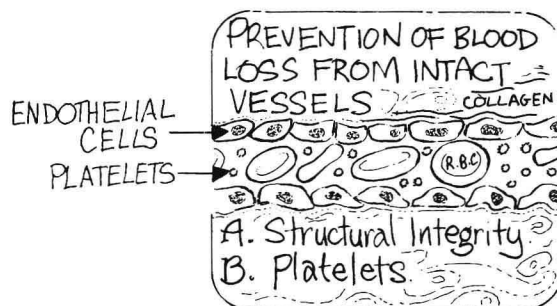
Chapter 1

An Introduction to Normal Hemostatic Mechanisms

Function of Hemostasis

1. Prevention of blood loss from intact vessels.
2. Arrest of bleeding from injured vessels.

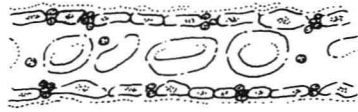
The function of the normal hemostatic mechanism is to prevent blood loss from intact vessels and to stop excessive bleeding from severed vessels.



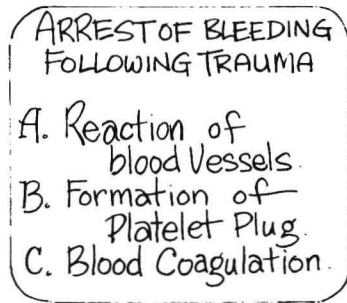
Blood loss from intact vessels is prevented by the structural integrity of the vessel walls, and by platelets. These factors are inter-related. Platelets nurture the endothelium and so contribute to its structural integrity.



When there are reduced numbers of platelets this nurturing does not take place and the endothelial cells have been shown to be remarkably thin.

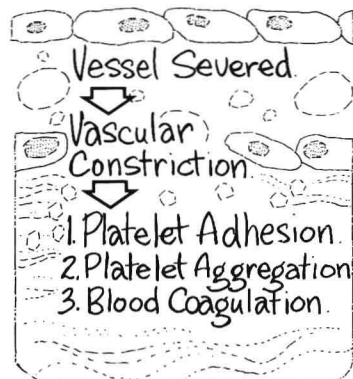


Platelets also adhere to the basement membrane when it is exposed by endothelial cell contraction, and so prevent plasma and cellular blood components from passing out of the blood vessels.



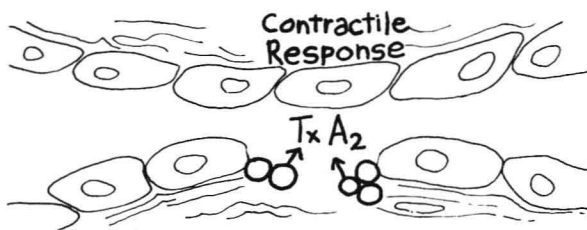
Arrest of bleeding following trauma is controlled by three interrelated factors. These three factors are the reaction of blood vessels to injury, the formation of the platelet plug at the site of injury, and the coagulation of blood.

Normal Hemostatic Mechanism

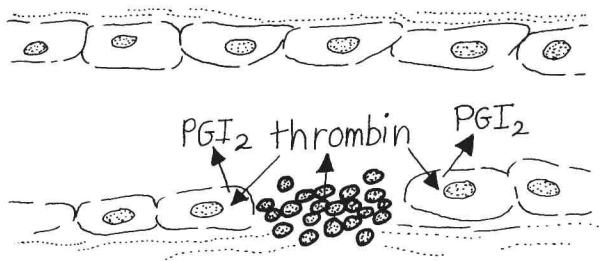


This is a simplified scheme of the normal hemostatic mechanism. When a vessel is severed it constricts, blood is shed, and the processes of platelet adhesion, platelet aggregation and blood coagulation are initiated.

Constriction of Vessels

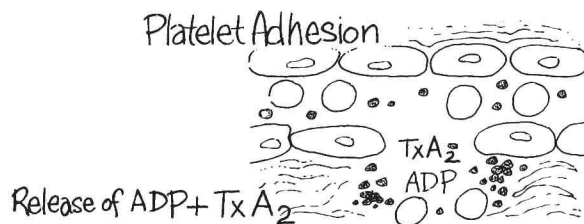


Vascular constriction is transient lasting for less than a minute. Two factors contribute to this; a local contractile response of the vascular wall cells to injury, and possibly also a powerful vasoconstrictor substance, thromboxane A₂, which is released from platelets at the site of injury.

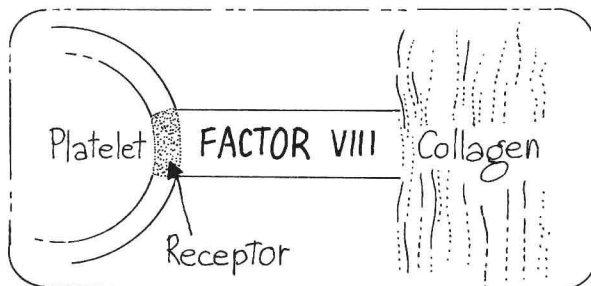


Later, under the influence of thrombin, injured vascular wall cells synthesize a powerful vasodilator substance, prostacyclin (PGI_2), which opposes the vasoconstrictive effect of thromboxane A_2 and so contributes to the transient nature of vessel wall constriction.

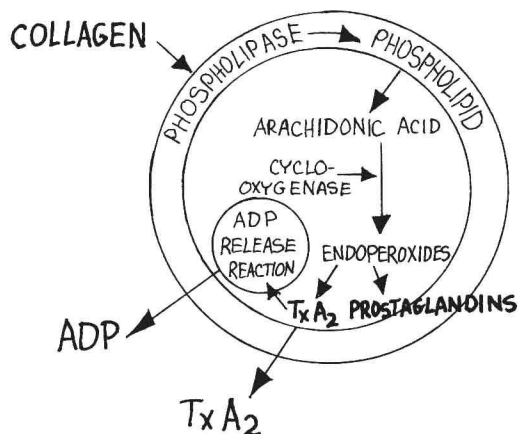
Formation of Unstable Platelet Plug



Following rupture of the vessel wall platelets adhere to the subendothelial connective tissue and to the basement membrane where they release adenosine diphosphate, and synthesize and release thromboxane A_2 , an end product of platelet prostaglandin synthesis.



The process of adhesion requires the presence of one of the clotting factors, von Willebrand's Factor VIII, and also normal platelet receptor sites for this molecule.

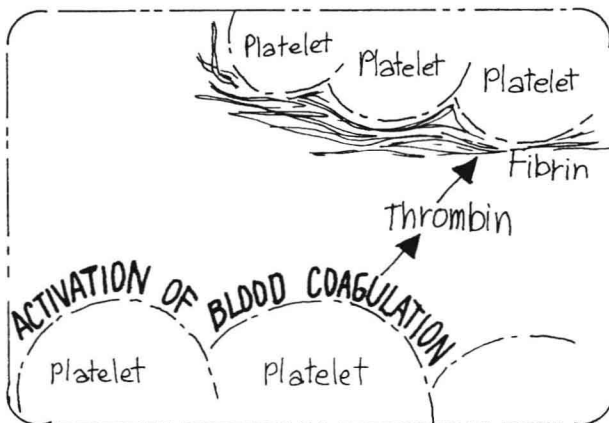


Contact with collagen induces the release of ADP and thromboxane A_2 from the platelets. This is dependent upon normal platelet prostaglandin synthesis.

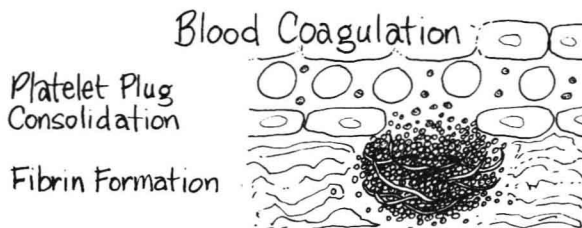


Both ADP and thromboxane A_2 stimulate platelets to aggregate and form an unstable platelet plug at the site of injury. The formation of the unstable platelet plug by the platelet aggregates takes place within seconds of vessel injury.

Stabilization of Plug with Fibrin

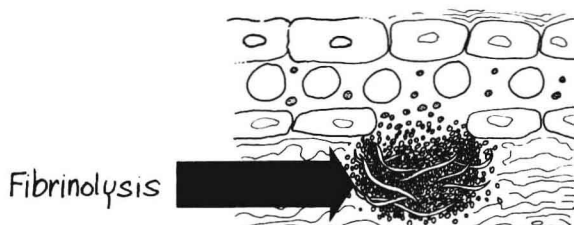


The aggregated platelets provide a surface on which blood coagulation occurs.



Fibrin, which is the final product of the blood coagulation process, consolidates the plug, rendering it stable. The unstable platelet plug is stabilized after a few minutes, but the fibrin component of the hemostatic plug gradually increases in amount as the platelets undergo autolysis, so that after 24 - 48 hours the hemostatic plug is completely transformed into fibrin.

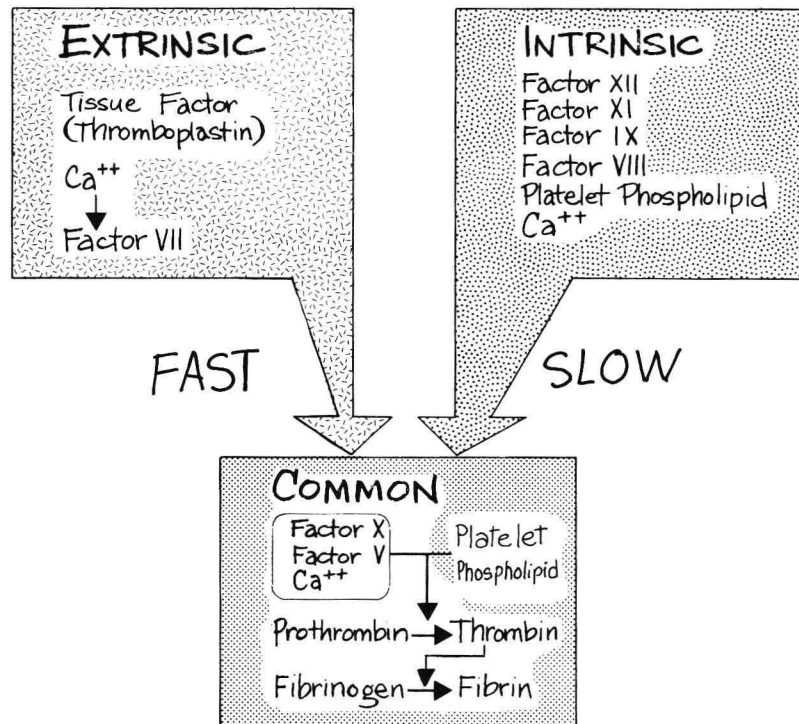
Fibrinolysis



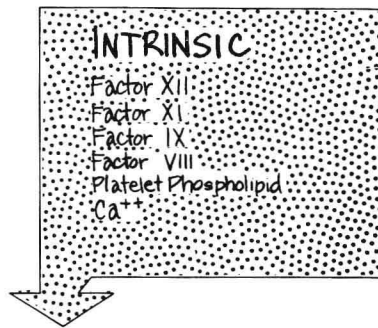
The fibrin is then digested by enzymes derived from the plasma (plasma fibrinolytic system) and from leucocytes and other cells (cellular fibrinolytic system) and the defect in the vessel wall is covered with endothelium.

Blood Coagulation

The process of blood coagulation occurs as a series of complex steps which terminate in the formation of a fibrin clot. Blood coagulation occurs either by activation of the intrinsic pathway, which is a relatively slow process, or the activation of the extrinsic pathway, which is a much faster process.

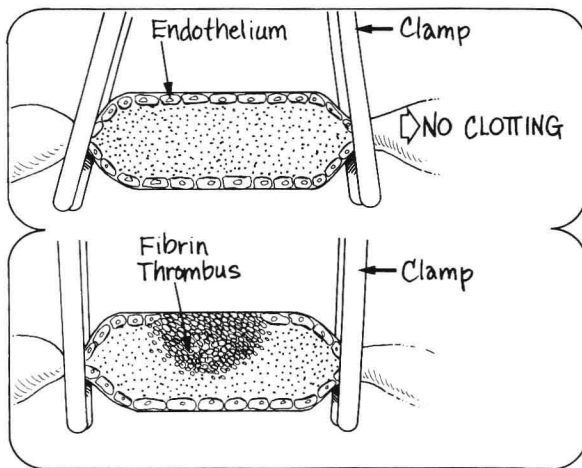


Intrinsic Clotting System



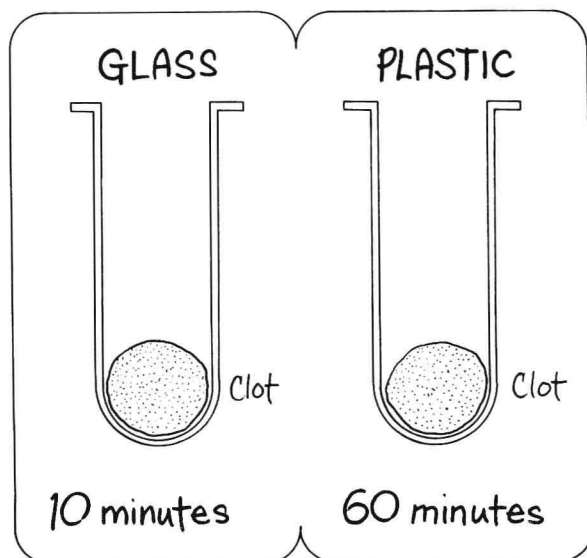
The intrinsic pathway will be considered first as this is the most important of the two systems. The intrinsic clotting system is activated when blood comes in contact with a foreign surface such as a prosthetic device, or damaged vessel wall. This can be demonstrated experimentally both in vivo and in vitro.

In Vivo



Activation of coagulation in vivo can be induced by minor vessel injury. If a segment of a vein is carefully isolated and clamped at both ends, the blood will remain fluid for days; this is shown in the upper diagram. On the other hand, if the endothelium of the vein is damaged, clotting will occur, because exposure of the subendothelial tissues to blood initiates clotting by activating Factor XII (ie. the Intrinsic Pathway) and possibly also by making tissue thromboplastin available, and thus activating the extrinsic pathway also.

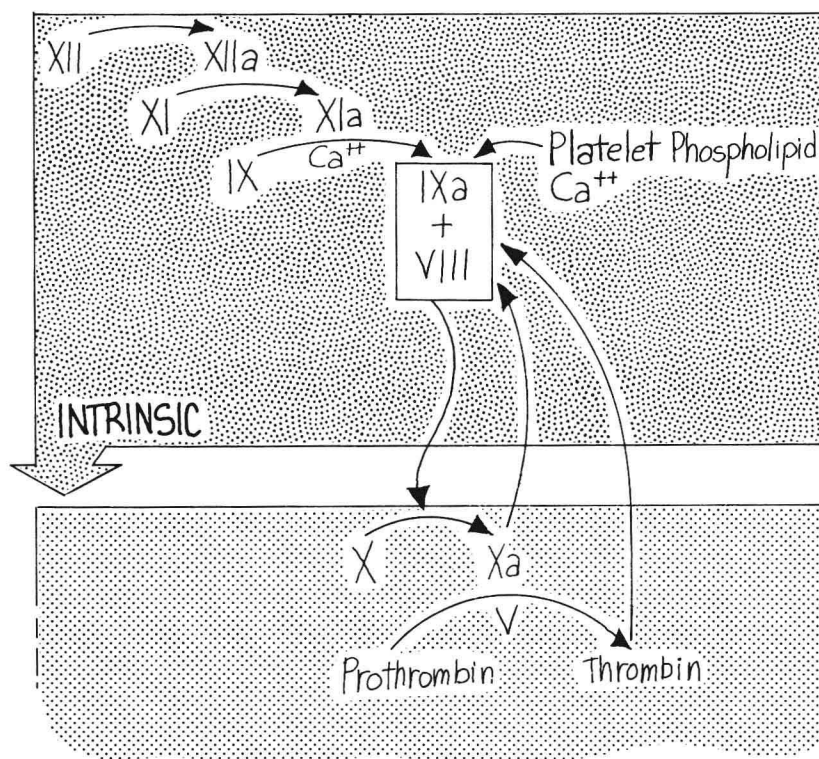
In Vitro



This experiment can also be performed in vitro. If the blood is drawn carefully and placed into a glass tube, the intrinsic clotting system is activated by contact of Factor XII with the glass tube, and clotting occurs in about 10 minutes. On the other hand, if the blood is exposed to a non-wettable surface such as plastic or siliconized glass, activation is less rapid and blood coagulation may be delayed for an hour or more. It seems, therefore that the non-wettable, plastic or siliconized glass surface behaves more like normal endothelium than the glass surface.

Activation of Intrinsic Pathway

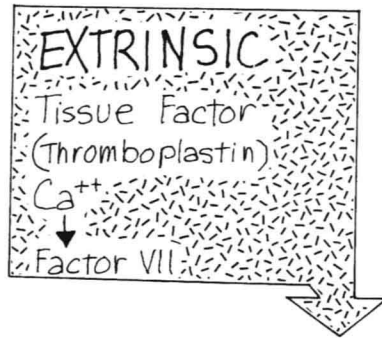
Activation of the intrinsic system is shown here. The coagulation factors circulate in the form of inactive precursors, some of these are pro-enzymes or zymogens and some of these are co-factors. Each zymogen is converted into an active form (the enzyme) and in turn activates the next clotting factor in the sequence. This concept has been likened to a cascade or water-fall.



Activation of the intrinsic pathway is initiated by conversion of the proenzyme Factor XII to its enzyme XIIa when blood comes into contact with a non-endothelialized surface such as a damaged vessel wall or prosthetic device. In vitro, Factor XII is activated by contact with the wall of the test tube. The activated Factor XII in turn converts the zymogen Factor XI to the enzyme Factor XIa,

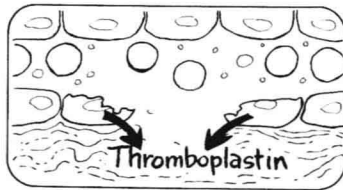
a reaction which is calcium-independent; all subsequent blood coagulation reactions require calcium. Factor XIa activates Factor IX and the Factor IXa in the presence of VIII and phospholipid activates Factor X. The rate of this reaction is greatly increased by the presence of phospholipid and by the prior exposure of Factor VIII to thrombin or Factor Xa.

Extrinsic Clotting System

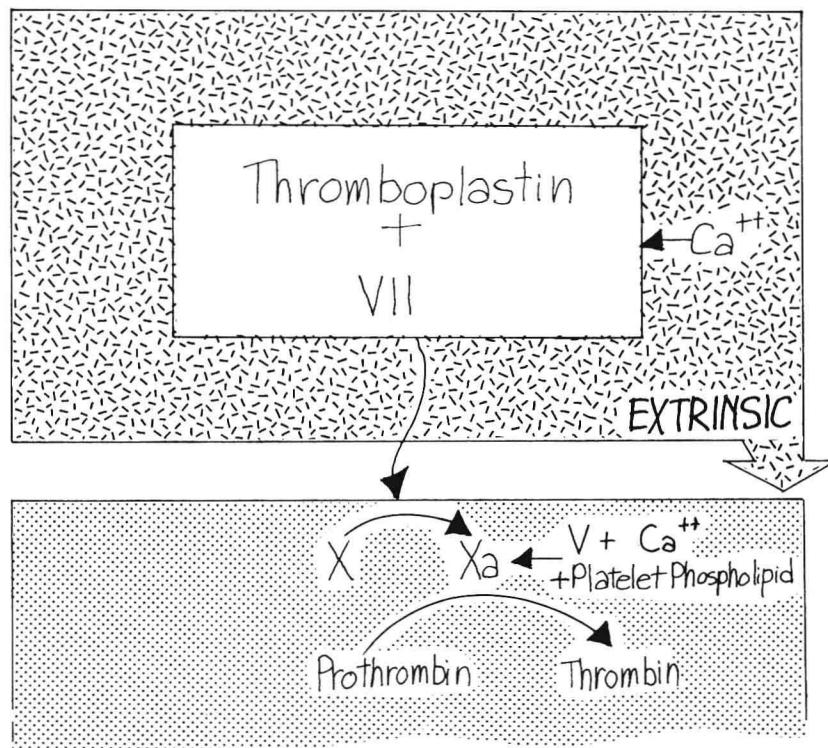


Consider now the extrinsic pathway. When extracts of various tissues such as brain or lung (known as thromboplastin) are added to blood, a number of early time-consuming steps in the intrinsic clotting system are bypassed, and coagulation occurs more rapidly as a result of the activation of the extrinsic system.

Activation of Extrinsic Pathway

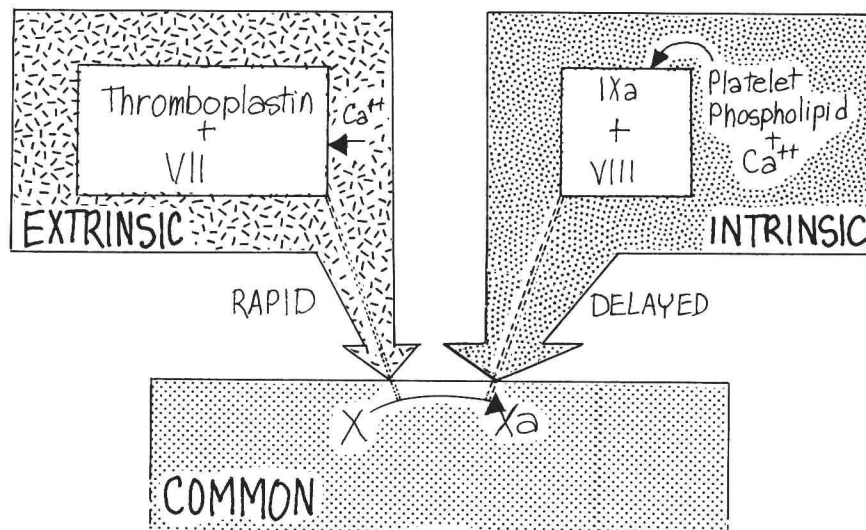


The extrinsic pathway is stimulated *in vivo* by exposure of blood to damaged endothelium or to extravascular tissues, both of which have been shown to have tissue thromboplastin material.

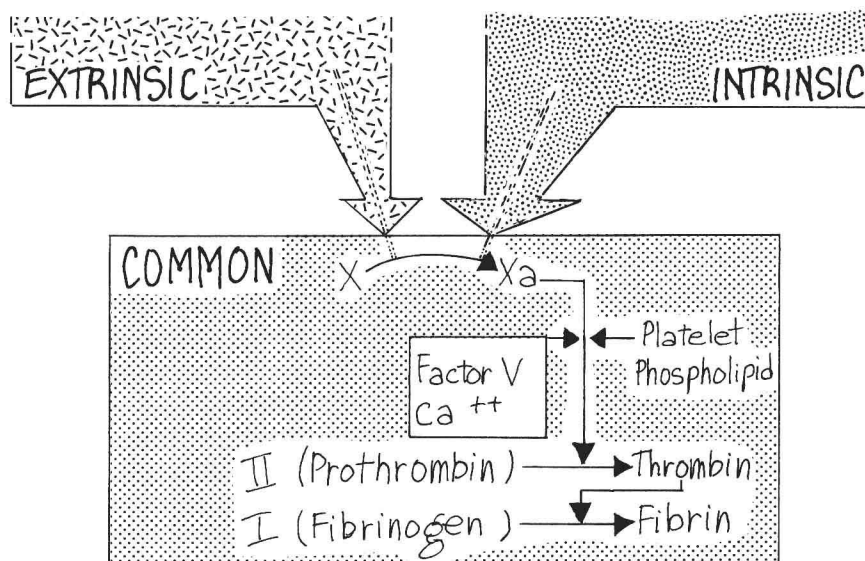


Thromboplastin forms a complex with Factor VII which in the presence of calcium activates Factor X.

Common Pathway



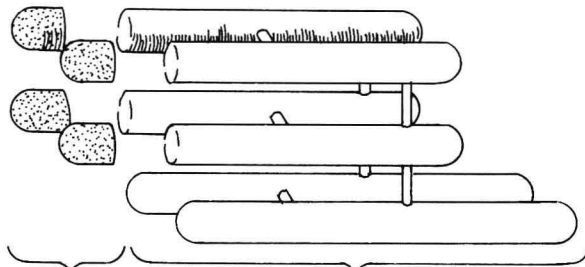
Factor X can be activated by either the complex of thromboplastin and Factor VII, or the complex of platelet phospholipid activated Factor IX and Factor VIII. As we have seen the extrinsic pathway is the most rapidly activated but the intrinsic although slower is probably the major contributor to the coagulation process.



The activated Factor X in the presence of calcium, Factor V and platelet phospholipid activates Factor II (prothrombin) which is cleaved to form thrombin. These reactions take place on the surface of the platelet in-

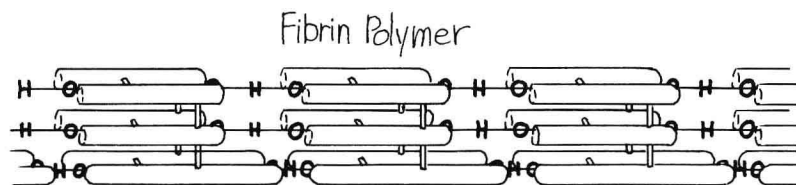
volving platelet phospholipid. Thrombin is detached from the platelet surface and converts Factor I (Fibrinogen) to fibrin in the plasma.

Fibrinogen to Fibrin

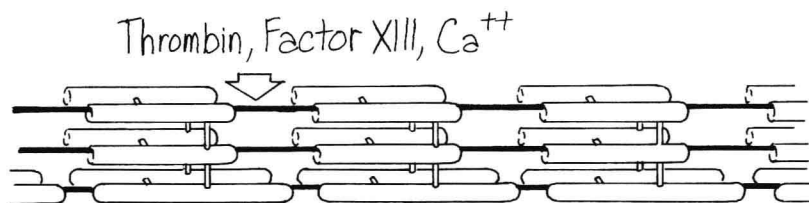


The first step is a limited proteolysis of fibrinogen by thrombin to form a fibrin monomer and the fibrinopeptides.

Fibrinopeptides - Fibrin Monomer +

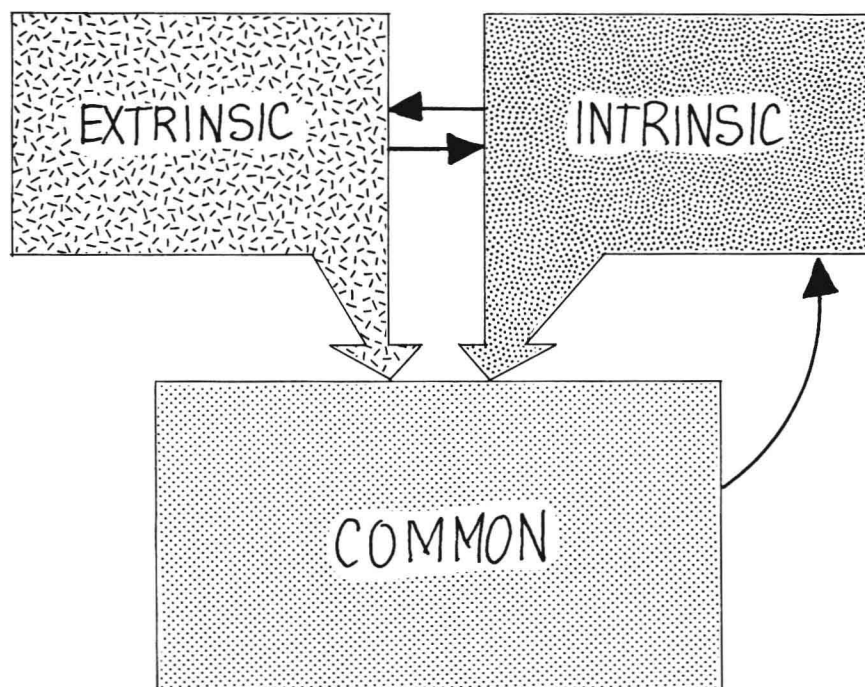


When the strongly electro-negative fibrinopeptides are cleaved from fibrinogen, fibrin monomer undergoes spontaneous polymerization to form a fibrin polymer. Initially, this is linked by hydrogen bonds,



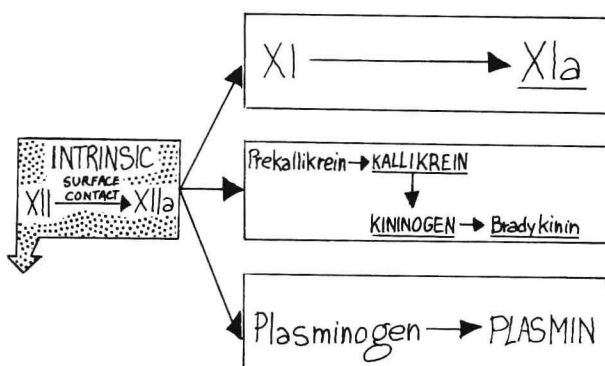
but in step III, the fibrin polymer is stabilized by covalent bonds. This step requires Factor XIII, thrombin, and calcium.

Feedback Loops

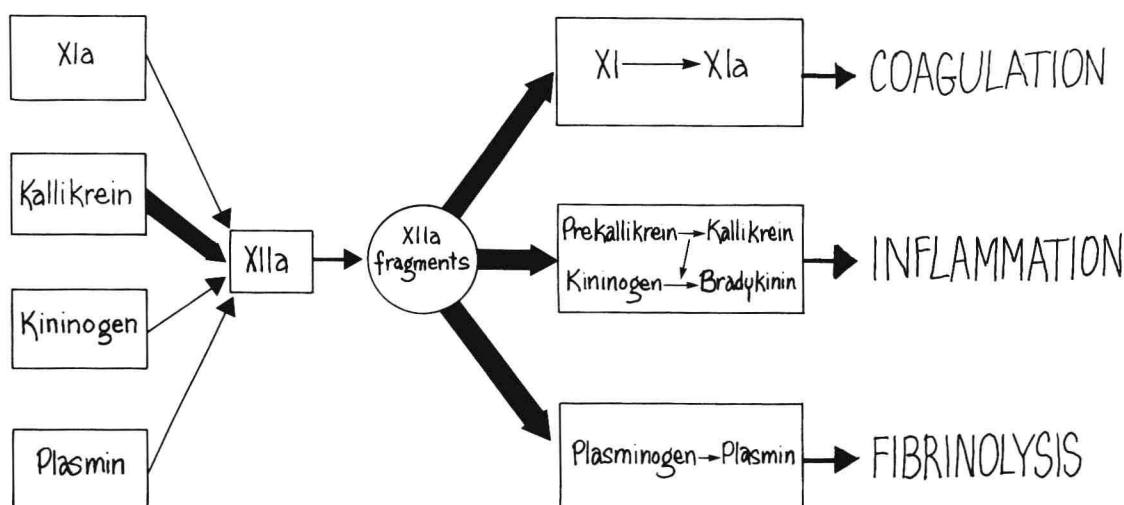


Blood coagulation is modified by a number of positive and negative feedback loops and by interaction between the three pathways. For example, from the common pathway, thrombin and Factor Xa, formed either by the activation of the extrinsic or intrinsic pathway, feed back to activate Factor VIII and Factor V and markedly accelerate the rate of the reactions in which these two coagulation factors are involved. Factor Xa feeds back to initially increase then to inhibit its own activation by Factor VIIa. The intrinsic and extrinsic pathways are also linked in a number of ways. Factor VII is activated by Factor IXa, XIIa, XIa and kallikrein and Factor VIIa can activate Factor IX directly. There is also evidence that the activation of Factor XI can occur independently of Factor XII through a platelet-related reaction. The ability of stimulated platelets to activate Factor XI directly probably explains the lack of a hemorrhagic diathesis in patients with Factor XII deficiency.

Role of Factor XII



Factor XII is partly activated by contact with a foreign surface in a non-proteolytic step, that is, the molecule is not cleaved. This form of activated XII is a relatively weak activator of a number of reactions, including activation of Factor XI. It also activates prekallikrein, an important step in the inflammatory response, and plasminogen which is the initial step leading to fibrinolysis.



The products of these reactions, particularly kallikrein, feed back to produce cleavage of the Factor XII molecule to Factor XII fragments. These Factor XII fragments are much more powerful activators of the subsequent steps, that is the conversion of Factor XI to XIa, prekallikrein to kallikrein and plasminogen to plasmin. All three of these proteolytic enzymes are capable of cleaving Factor XII to form Factor XIIa fragments which are much more effective in inducing the formation of activated Factor XI, of kallikrein and of plasmin. Kallikrein also converts kininogen to bradykinin and it appears that kininogen also plays a role in Factor XII activation.

Support for the role of prekallikrein and kininogen in Factor XII activation is provided by studies of families with deficiencies in prekallikrein (also known as Fletcher Factor after the first family with this defect) and kininogen (also known as Fitzgerald Factor after the first family). In both instances there is impaired surface activation of Factor XII with a corresponding prolongation of the in vitro coagulation tests.