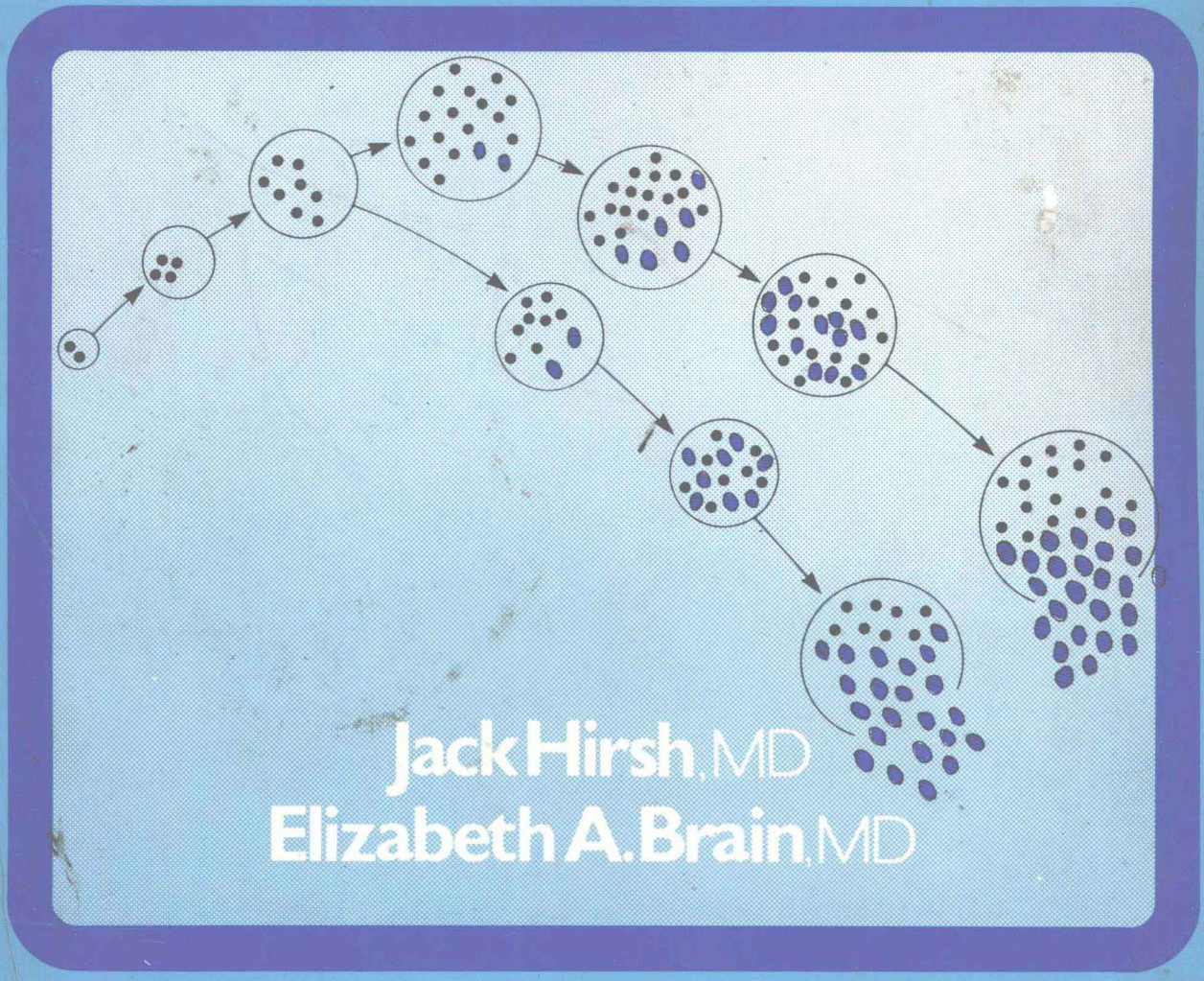
HEMOSTASIS & THROMBOSIS

A CONCEPTUAL APPROACH

Second Edition



Jack Hirsh, MD
Elizabeth A. Brain, MD

Churchill Livingstone

HEMOSTASIS & THROMBOSIS

A CONCEPTUAL APPROACH

SECOND EDITION

JACK HIRSH, M.D.
Professor and
Chairman of the Department of Medicine
Faculty of Health Sciences
McMaster University
Hamilton, Ontario, Canada

ELIZABETH A. BRAIN, M.D.
Learning Resources Editor
Faculty of Health Sciences
McMaster University
Hamilton, Ontario, Canada

Produced through the facilities of
McMaster University Audiovisual Services

Illustrated by
Knud C. Skov
Molly Pulver
Anna Hirsh

Typesetting
Vicky Bach

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

Second Edition

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

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.

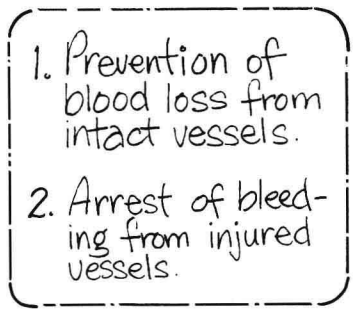
May 1982

Table of Contents

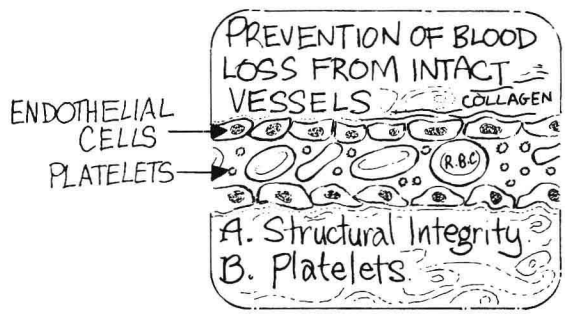
Chapter 1

An Introduction to Normal Hemostatic Mechanisms

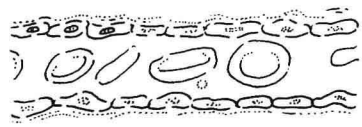
Function of Hemostasis



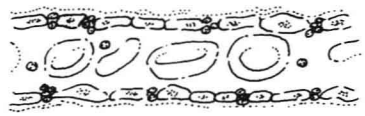
The function of the normal hemostatic mechanism is to prevent blood loss from intact vessels and to stop excessive bleeding from severed vessels.



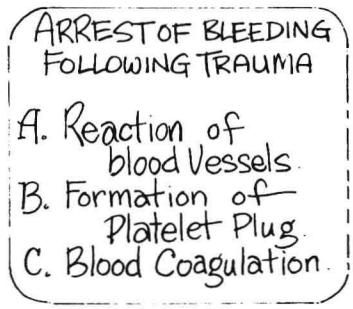
Blood loss from intact vessels is prevented by the structural integrity of the vessel walls, and by platelets. These factors are interrelated. Platelets nurture the endothelium and so contribute to its structural integrity.



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

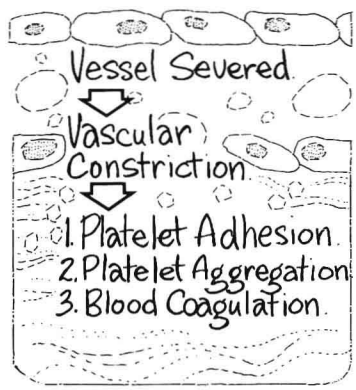


Platelets also adhere to the basement membrane when it is exposed by endothelial cell contraction, and so prevent plasma and cellular blood components from passing out of the blood vessels.



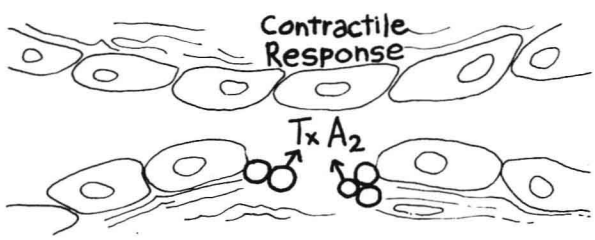
Arrest of bleeding following trauma is controlled by three interrelated factors. These three factors are the reaction of blood vessels to injury, the formation of the platelet plug at the site of injury, and the coagulation of blood.

Normal Hemostatic Mechanism

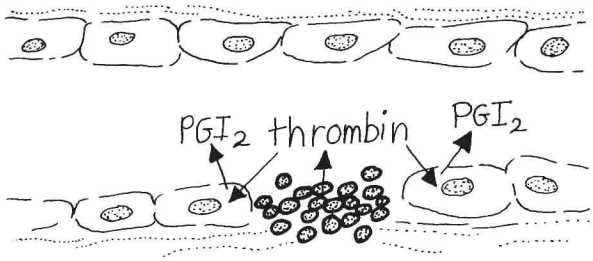


This is a simplified scheme of the normal hemostatic mechanism. When a vessel is severed it constricts, blood is shed, and the processes of platelet adhesion, platelet aggregation and blood coagulation are initiated.

Constriction of Vessels

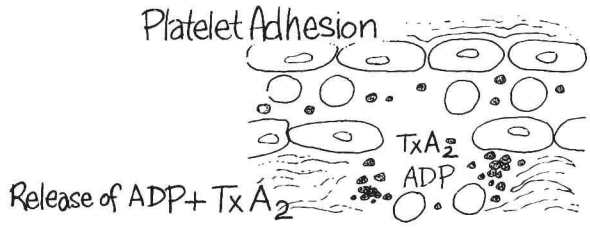


Vascular constriction is transient lasting for less than a minute. Two factors contribute to this; a local contractile response of the vascular wall cells to injury, and possibly also a powerful vasoconstrictor substance, thromboxane A_2, which is released from platelets at the site of injury.

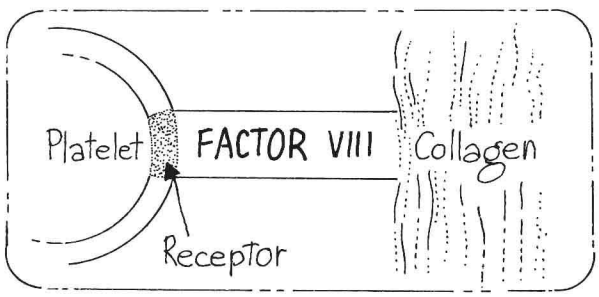


Later, under the influence of thrombin, injured vascular wall cells synthesize a powerful vasodilator substance, prostacyclin (PGI_2), which opposes the vasoconstrictive effect of thromboxane A_2 and so contributes to the transient nature of vessel wall constriction.

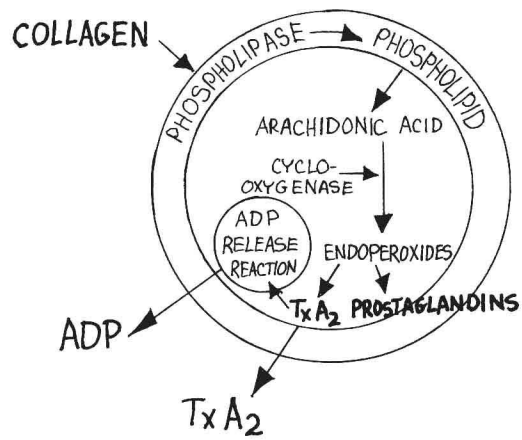
Formation of Unstable Platelet Plug



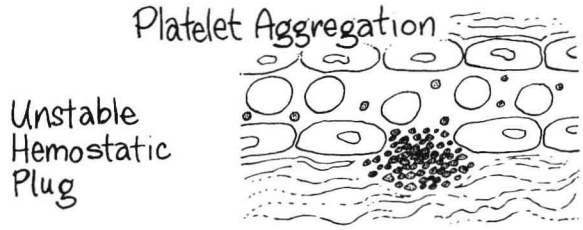
Following rupture of the vessel wall platelets adhere to the subendothelial connective tissue and to the basement membrane where they release adenosine diphosphate, and synthesize and release thromboxane A_2, an end product of platelet prostaglandin synthesis.



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.

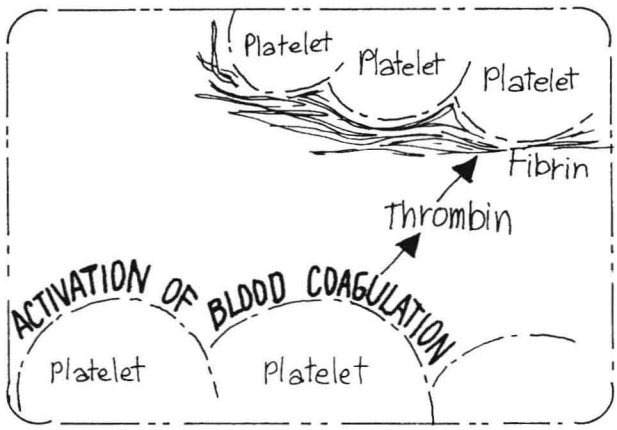


Contact with collagen induces the release of ADP and thromboxane A_2 from the platelets. This is dependent upon normal platelet prostaglandin synthesis.

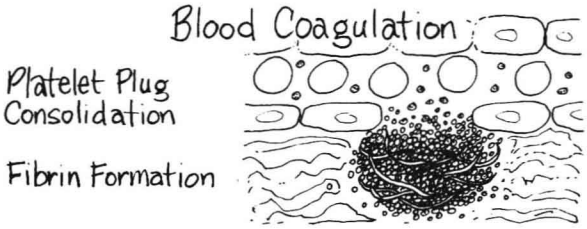


Both ADP and thromboxane A_2 stimulate platelets to aggregate and form an unstable platelet plug at the site of injury. The formation of the unstable platelet plug by the platelet aggregates takes place within seconds of vessel injury.

Stabilization of Plug with Fibrin

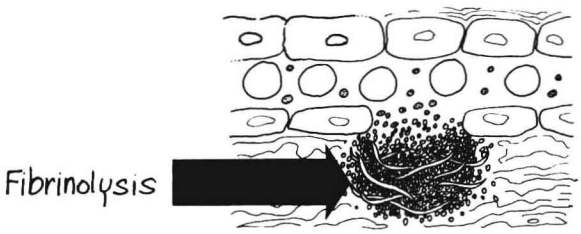


The aggregated platelets provide a surface on which blood coagulation occurs.



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.

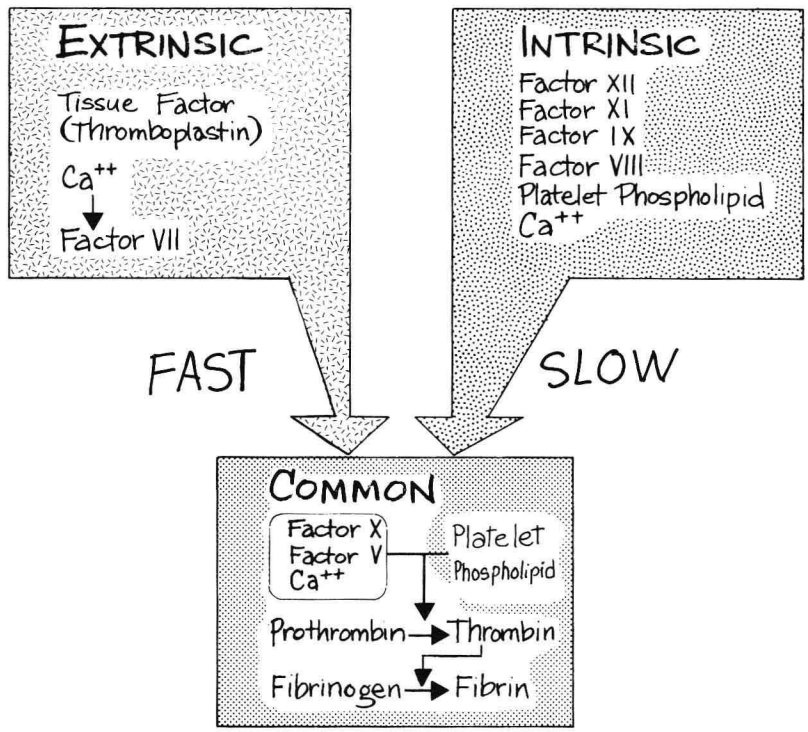
Fibrinolysis



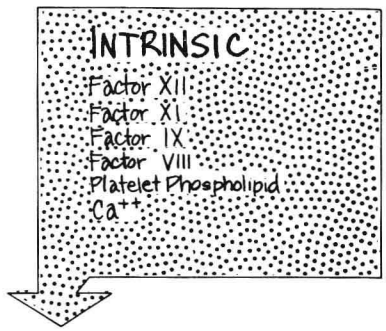
The fibrin is then digested by enzymes derived from the plasma (plasma fibrinolytic system) and from leucocytes and other cells (cellular fibrinolytic system) and the defect in the vessel wall is covered with endothelium.

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.

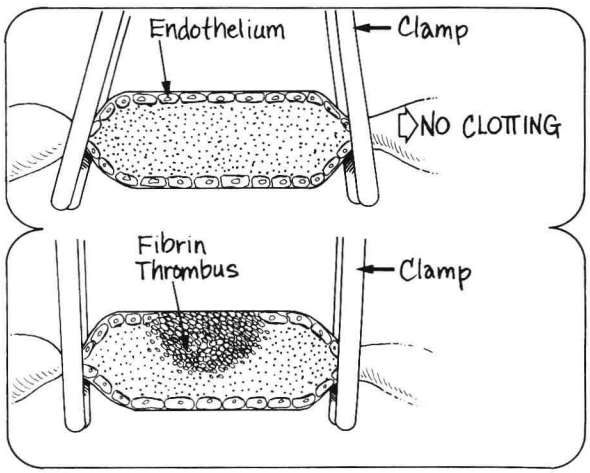


Intrinsic Clotting System



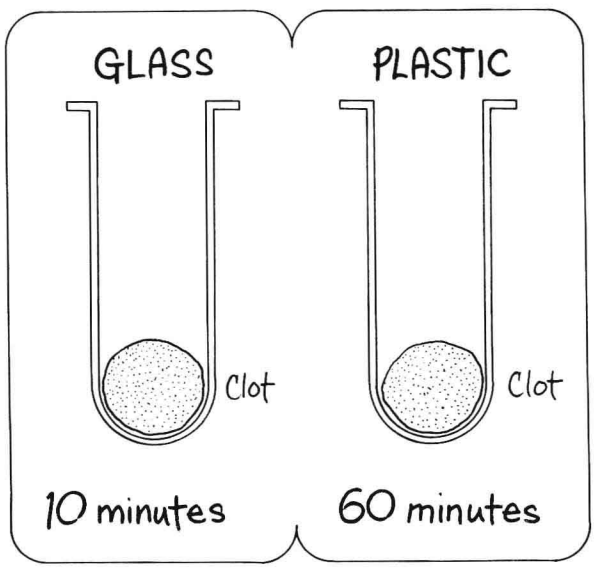
The intrinsic pathway will be considered first as this is the most important of the two systems. The intrinsic clotting system is activated when blood comes in contact with a foreign surface such as a prosthetic device, or damaged vessel wall. This can be demonstrated experimentally both in vivo and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

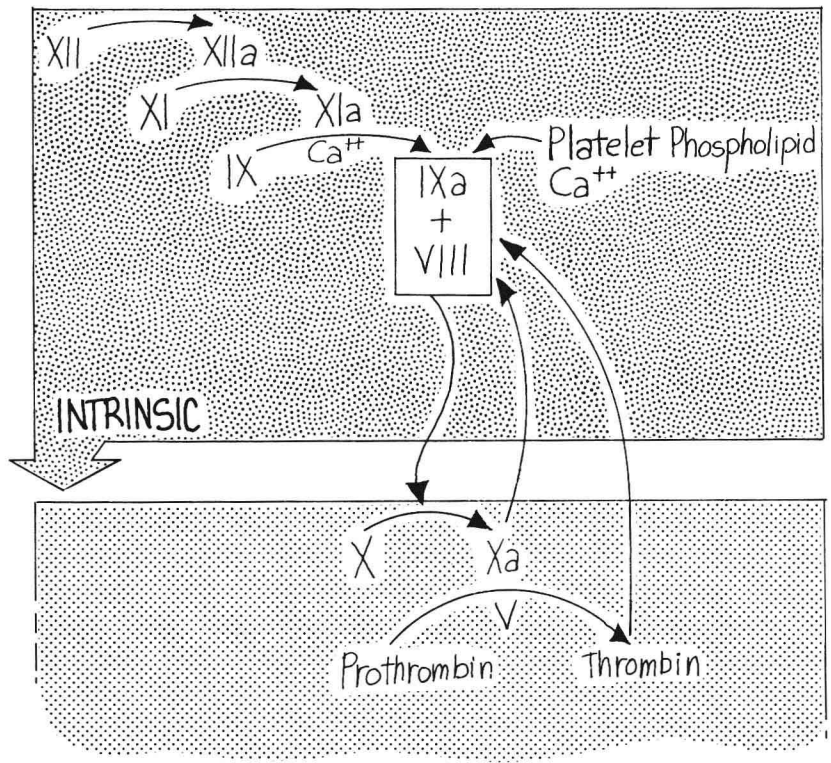
In Vitro



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.

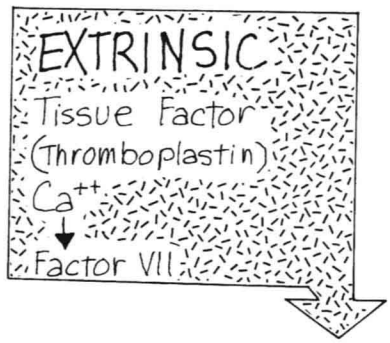
Activation of Intrinsic Pathway

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.



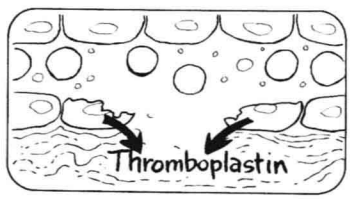
Activation of the intrinsic pathway is initiated by conversion of the proenzyme Factor XII to its enzyme XIIa when blood comes into contact with a non-endothelialized surface such as a damaged vessel wall or prosthetic device. In vitro, Factor XII is activated by contact with the wall of the test tube.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

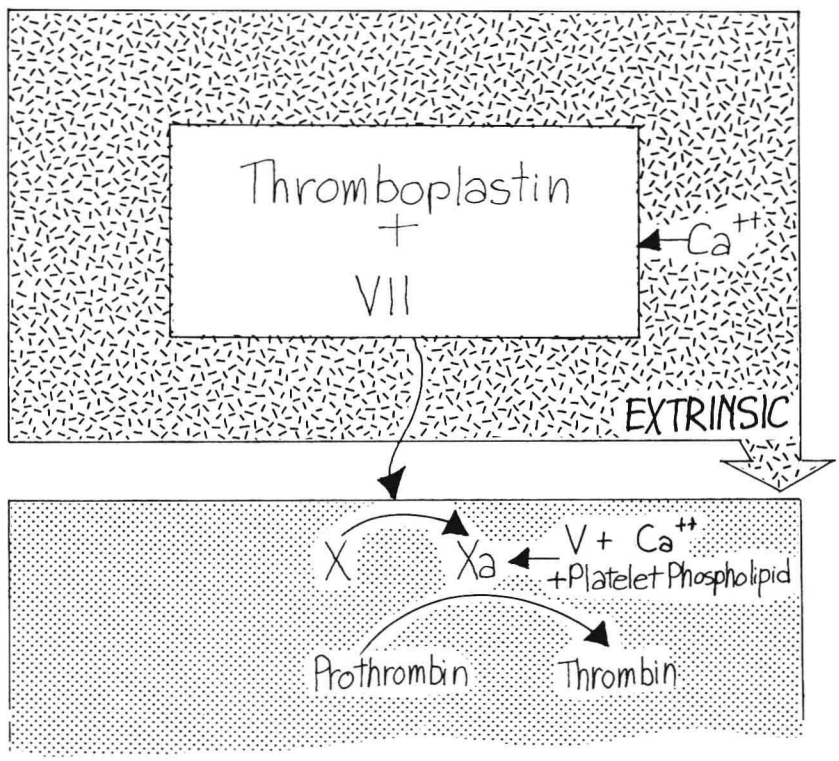


Consider now the extrinsic pathway. When extracts of various tissues such as brain or lung (known as thromboplastin) are added to blood, a number of early time-consuming steps in the intrinsic clotting system are by-passed, and coagulation occurs more rapidly as a result of the activation of the extrinsic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

Activation of Extrinsic Pathway

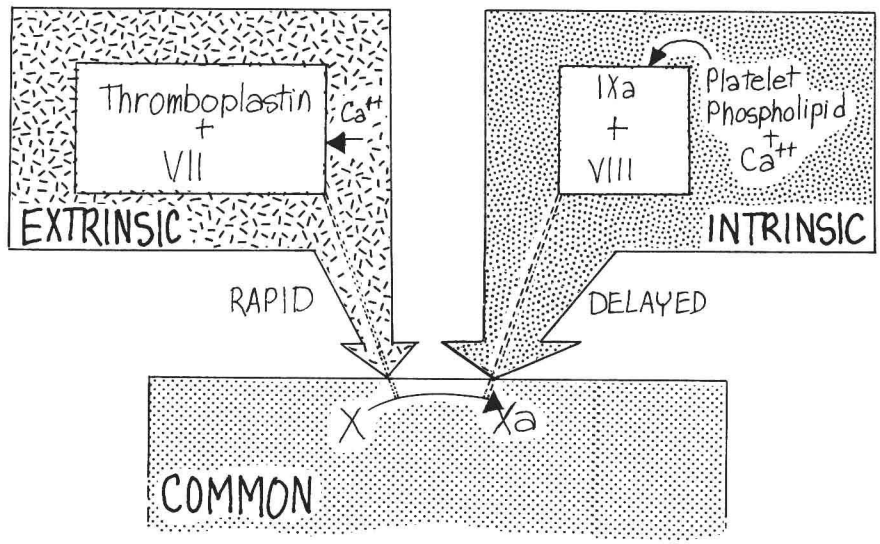


The extrinsic pathway is stimulated in vivo by exposure of blood to damaged endothelium or to extravascular tissues, both of which have been shown to have tissue thrombo-plastin material.

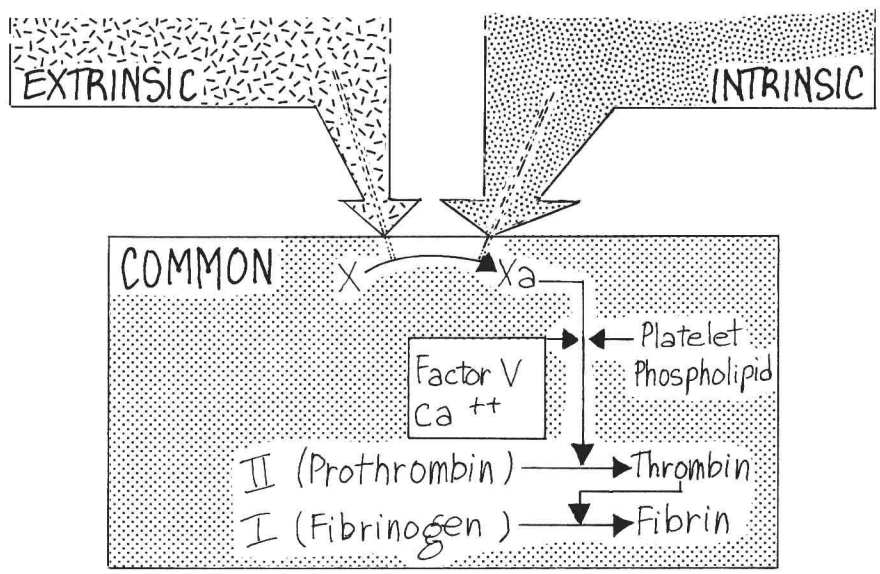


Thromboplastin forms a complex with Factor VII which in the presence of calcium activates Factor X.

Common Pathway

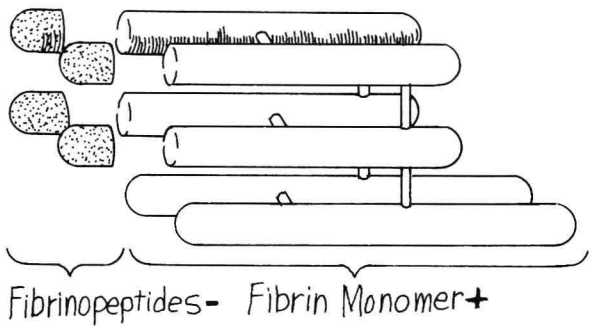


Factor X can be activated by either the complex of thromboplastin and Factor VII, or the complex of platelet phospholipid activated Factor IX and Factor VIII. As we have seen the extrinsic pathway is the most rapidly activated but the intrinsic although slower is probably the major contributor to the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

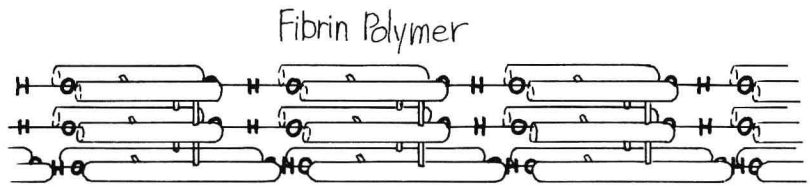


The activated Factor X in the presence of calcium, Factor V and platelet phospholipid activates Factor II (prothrombin) which is cleaved to form thrombin. These reactions take place on the surface of the platelet involving platelet phospholipid. Thrombin is detached from the platelet surface and converts Factor I (Fibrinogen) to fibrin in the plasma.

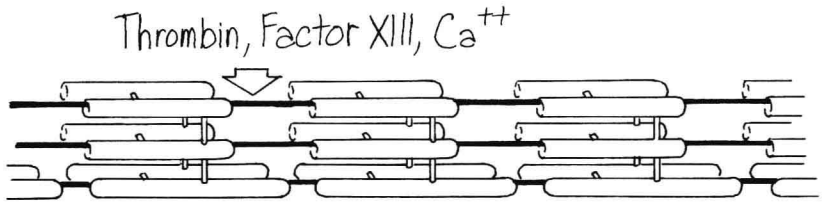
Fibrinogen to Fibrin



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

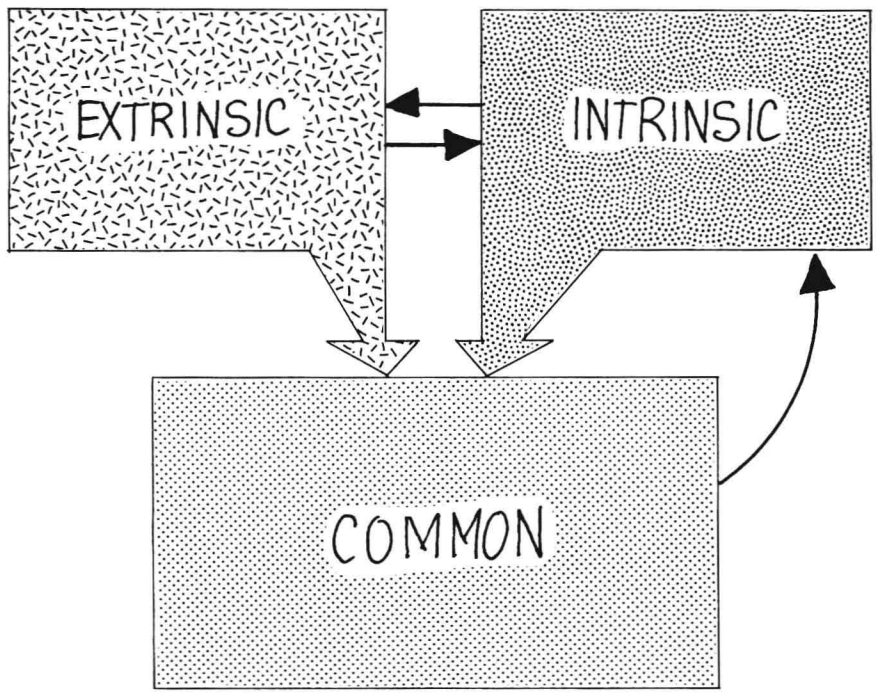


When the strongly electro-negative fibrinopeptides are cleaved from fibrinogen, fibrin monomer undergoes spontaneous polymerization to form a fibrin polymer. Initially, this is linked by hydrogen bonds,



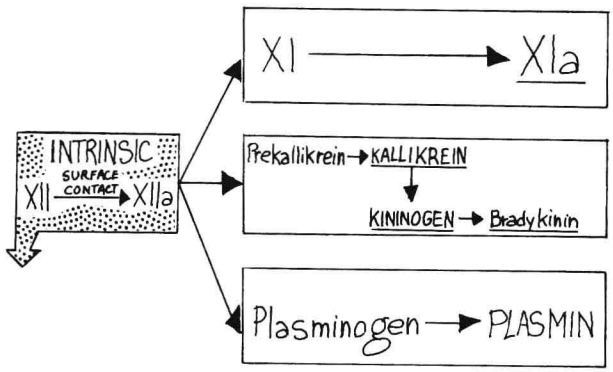
but in step III, the fibrin polymer is stabilized by covalent bonds. This step requires Factor XIII, thrombin, and calcium.

Feedback Loops

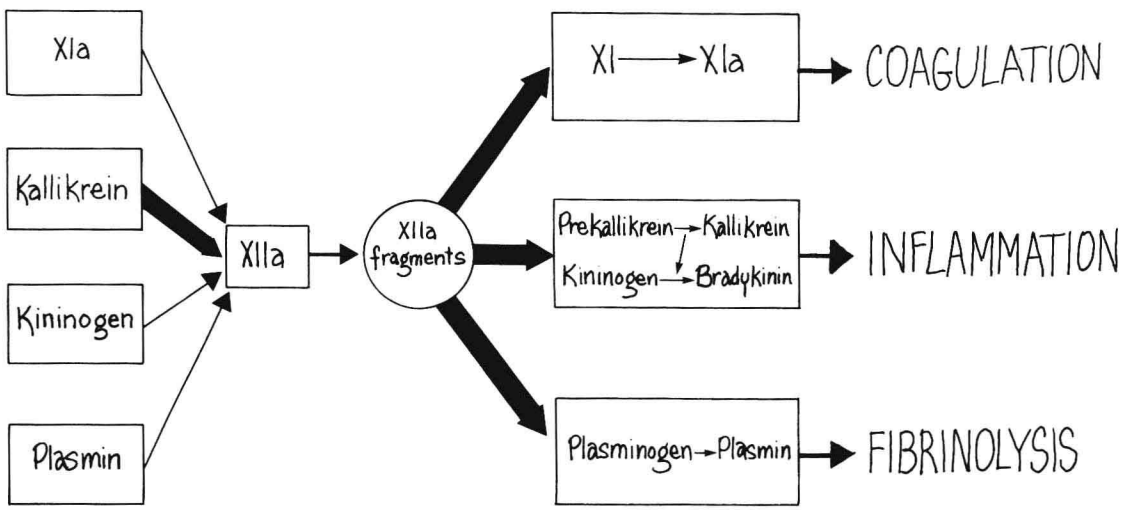


Blood coagulation is modified by a number of positive and negative feedback loops and by interaction between the three pathways. For example, from the common pathway, thrombin and Factor Xa, formed either by the activation of the extrinsic or intrinsic pathway, feed back to activate Factor VIII and Factor 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.