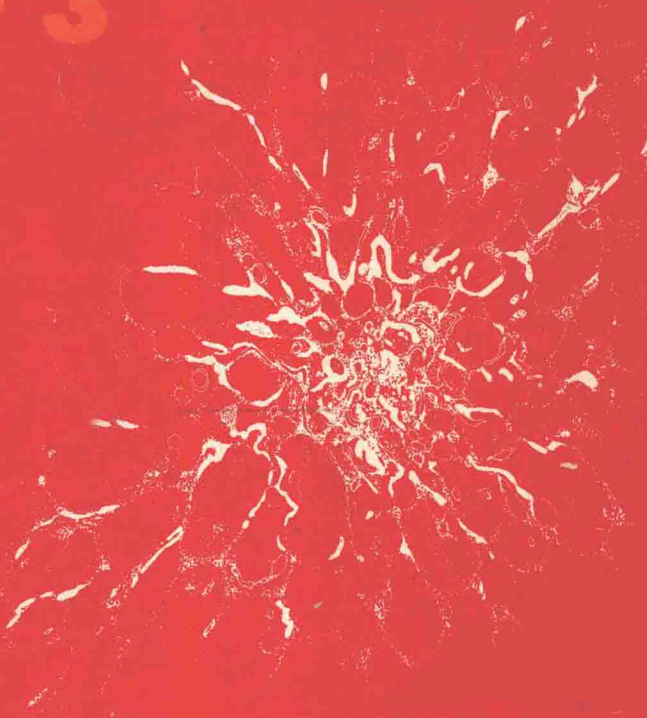
Manual of Hemostasis and Thrombosis

edition 3



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F. A. DAVIS COMPANY • Philadelphia

Printed in the United States of America

Library of Congress Cataloging in Publication Data

Thompson, Arthur R.
Manual of hemostasis and thrombosis.

Rev. ed. of: Hemostasis manual / Laurence A. Harker, Ed. 2. 1974.
Includes bibliographical references and index.
1. Hemostasis—Handbooks, manuals, etc. 2. Thrombosis—Handbooks, manuals, etc. I. Harker, Laurence A. Hemostasis manual. II. Title.
[DNLM: 1. Hemostasis. 2. Thrombosis. 3. Blood coagulation disorders. WH 310 T468m]
RB144.T45 1982 616.1'3 82-14871
ISBN 0-8036-8481-9

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PREFACE

The purpose of this manual is to describe a pathophysiologic approach to the diagnosis and management of patients with hemostatic and thrombotic disorders. Since the approach is designed for students, house officers, physicians and other health professionals seeking an updated, concise review of this subject, the book is divided into sections. Fundamental concepts of hemostasis and thrombosis are presented in Section I. The clinical application of these fundamentals with regard to hemostatic disorders is presented in Section II, and, to thrombotic disorders, in Section III. Our intent is to provide in a single volume the source material needed throughout training and as a review. We have chosen to document the book with recent selected citations from the literature for two reasons. First, it is important to establish the scientific basis for the approach, and second, we feel that it is appropriate to date the current formulation, and thereby emphasize the inevitable evolution that must occur as the field develops in the years to come.

We are indebted to our associates who have contributed much to this work. In particular, we would like to acknowledge the intellectual input from Drs. Samuel A. Burstein, Richard B. Counts, John M. Harlan, and Thomas W. Malpass. We also express special appreciation to Paul Su for his art work, Lisa Jones for her editorial and secretarial help, Ruth Henderson for her technical assistance, together with Daphne Matlick and Lou Limtiaco for invaluable secretarial assistance.

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PART 1

CONCEPTS OF HEMOSTASIS AND THROMBOSIS

The hemostatic mechanism is designed to arrest bleeding from vessels that have undergone a break in their integrity. The process is rapid and localized without compromising fluidity of the blood in circulation. Hemostasis involves a complex integrated interaction of (1) blood vessel, (2) platelets, and (3) coagulation cascade to form a localized stable mechanical seal that subsequently undergoes slow removal by (4) fibrinolysis. Rapid, localized hemostasis within a fluid medium is achieved by complicated systems of activation and inhibition whereby excessive bleeding and unwanted thrombosis are minimized. In this section, the components of the hemostatic mechanism will be considered with regard to their normal structure, function, interrelationships, and the mechanisms of their activation and inhibition.

1

BLOOD VESSELS AND ENDOTHELIUM

STRUCTURE

Metabolic exchange depends upon the flow of blood through thin-walled capillaries. Their structure consists of a supportive basement membrane to which endothelial cells are tightly anchored (Fig. 1). Endothelial cells form a continuous monolayer that lines all blood vessels. However, endothelia differ in structure, function, and metabolic behavior in different organs, different parts of the same organ, and different segments of a single microcirculatory loop.[1] In general, the morphology predicts barrier function, and accordingly endothelium is classified as being (1) continuous, showing gap or tight intercellular junctions; (2) fenestrated; or (3) discontinuous. Continuous tight junctional endothelium is typical of the cerebral circulation, whereas fenestrated endothelium is illustrated by hepatic sinusoids.[2]

The larger vessels of the microcirculation (arterioles and venules) have a more complete structure consisting of: (1) the inner intima, including endothelium and subendothelium (basement membrane, elastic tissue, collagen fibers); (2) media composed of smooth muscle cells, collagen fibers, and occasional fibroblasts; and (3) the outer adventitia, consisting of fibroblasts and collagen fibers. As vascular size increases, noncollagenous microfibrils appear in the subendothelium and the elastic components condense into the well-defined internal elastic lamina, which separates the media from the intima.

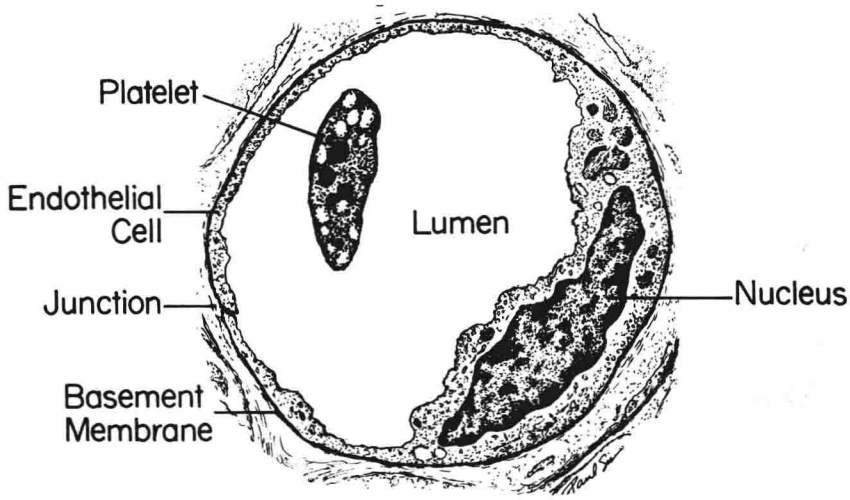

FIGURE 1. Structure of blood vessels. Vascular endothelium forms a cellular monolayer that interfaces between blood and the underlying tissues. Endothelial cells function in the (a) transfer of metabolic substances, (b) formation of a barrier between the subendothelium and blood cells and macromolecules, (c) synthesis or metabolism of blood and subendothelial mediators, (d) thromboresistance of the vessel toward flowing blood, (e) repair processes, and (f) cellular immunity.

FUNCTION

Endothelial cells perform a number of critical functions including: (1) the material transfer of metabolic substances of varied molecular size between the circulating blood and the surrounding tissues; (2) the formation of a relative barrier to blood cells, plasma macromolecules, and particulate material; (3) the synthesis or metabolism of mediators that regulate the interaction between the vessel wall and blood components, for example, factor VIII/vWF, fibronectin, collagen, proteoglycans, and labile mediators of vascular tone; (4) the maintenance of thromboresistance; (5) mediation of vascular repair processes, such as cell migration, proliferation and thrombolysis; and (6) the processing of antigen in cellular immunity.[1-4]

The exchange of materials across the endothelium involves movement by active vesicles, transendothelial channels, or intercellular clefts. Maintaining the integrity of the vessel wall to the egress of blood cells depends upon the barrier function of the endothelium and the underlying vascular connective tissue, together with platelets that seal over gaps in the endothelial lining.[1]

One of the basic functional characteristics of intact, normal endothelium is its nonreactivity to platelets, leukocytes, and the coagulation factors. The thromboresistant character of the endothelium involves both passive and ac-

tive mechanisms. The endothelial proteoglycans, primarily heparan sulfate, provide a surface that is passively nonthrombogenic.[5] Active thromboresistance of the endothelium is achieved through several mechanisms, including (1) the synthesis and release of prostacyclin (PGI_2); (2) secretion of plasminogen activators; (3) degradation of proaggregatory adenosine 5'-diphosphate (ADP) by membrane-associated apyrase (ADPase); (4) uptake and degradation of proaggregatory vasoactive amines; (5) uptake, inactivation, and clearance of thrombin; and (6) contribution of a cofactor (thrombomodulin) in the thrombin-dependent activation of protein C. The latter results in destruction of coagulation factors V and VIII and the release of plasminongen activators.[6-12]

PGI_2 is a labile prostaglandin that potently inhibits platelet adhesion and aggregation (Fig. 2). Modulation of PGI_2 production by injury factors, including activated clotting enzymes, serves to limit locally any hemostatic response.[13] The capacity of the endothelial lining to regulate PGI_2 production contributes to the nonthrombogenic properties of intact vascular endothelium. Endothelial denudation results in a loss of the nonthrombogenic surface as well as exposure of subendothelial connective structures to circulating blood.

The endothelium produces its own underlying connective tissue composed of several classes of collagen, proteoglycans, elastin, and microfibrils.[1,2] This connective tissue matrix modulates the permeability of the inner vessel wall and provides the principal stimulus to thrombosis following vessel injury.

Endothelial disruption activates directly all four components of the hemostatic apparatus: (1) Rapid vasoconstriction involves a direct vasoconstrictive response of the injured vessel and reflex stimulation of adjacent vessels. Reduced blood loss promotes more effective contact-activation of platelets and coagulation. Although vasoconstriction is not required for hemostasis to occur, it is critical in preventing exsanguination following severance of large vessels, especially arteries. (2) Platelets adhere immediately to exposed subendothelial connective tissue structures, particularly collagen fibers. Adherent and aggregated platelets enhance vasoconstriction by releasing thromboxane A_2 and vasoactive amines, including serotonin and epinepherine. (3) Coagulation is initiated both through the intrinsic system and the extrinsic system. (4) Fibrinolysis follows the release of tissue plasminogen activators from the vascular wall. Fibrinolytic removal of excess hemostatic material is necessary to reestablish vascular patency.

The relative importance of these reactions varies with vessel size. Capillaries, once ruptured, seal directly and immediately with little dependence on hemostasis. Breaks in arterioles and venules, on the other hand, become quickly occluded with a mass of fused platelets. Veins, which contain about 70 percent of the blood volume, may rupture with only modest trauma when subjected to increased hydrostatic pressure; hemostasis depends upon vascular contraction as well as perivascular and intravascular activation of hemostatic factors. Although arteries are the most resistant of all vessels to bleeding because of their thick, muscular walls, major trauma or erosive disease may precipitate arterial hemorrhage—the most severe test of hemostasis. Vasocon-

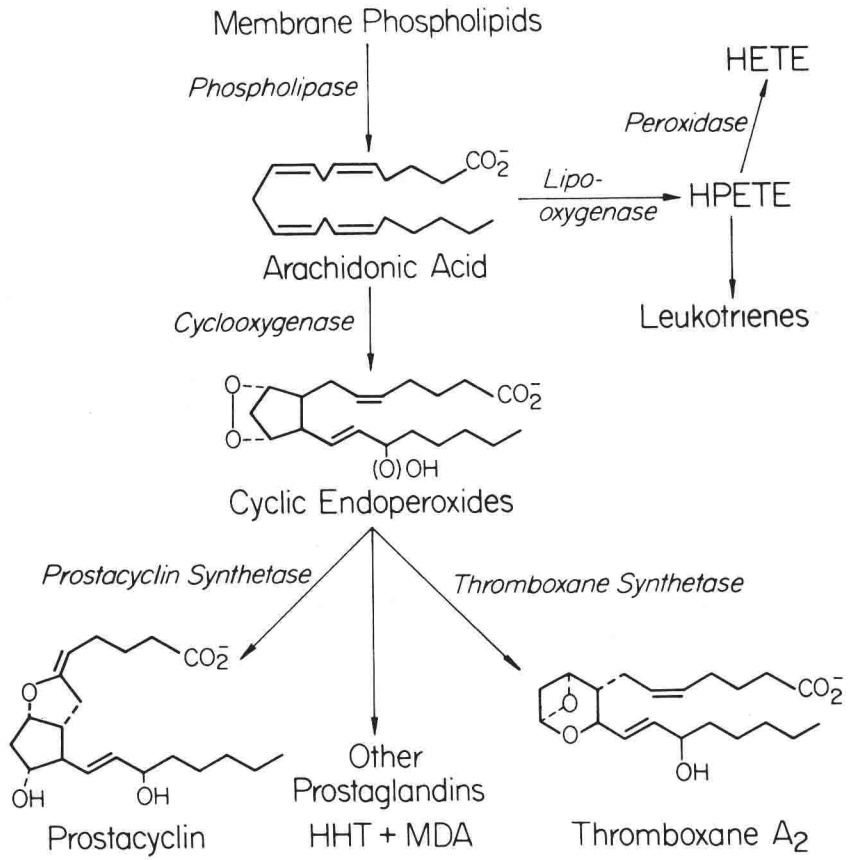

FIGURE 2. Prostaglandin metabolism. Phospholipase cleaves arachidonic acid-esters.[13] In the platelet, this enzyme is stimulated by low concentrations of ionized (non-bound) calcium, being further regulated by intracellular magnesium ion and cyclic AMP levels. Arachidonic acid is converted by an aspirin-sensitive cyclooxygenase to cyclic endoperoxides PGG_2 and PGH_2, or by a lipoxygenase to 12L-hydroxy-eicosatetraenoic acid (HETE) from its hydroperoxy intermediate (HPETE); the latter is also converted to leukotrienes. In the endothelial cell, these highly unstable cyclic endoperoxides are converted to PGI_2 (prostacyclin), a potent inhibitor of platelet aggregation and a vasodilator that is rapidly degraded to 6-keto-$PGF_{1\alpha}$ in vitro and multiple other metabolites in vivo. Within the platelet, thromboxane A_2 (TxA_2) is formed but spontaneously hydrolyzes to the stable, inactive, TxB_2. Thromboxane A_2 mediates vasoconstriction as well as platelet aggregation and release. PGG_2/PGH_2 are nonenzymatically transformed to 12L-hydroxy-5,8,10-heptadecatrienoic acid (HHT) and malondialdehyde (MDA) or the stable prostaglandins PGD_2, PHE_2, and PGF_2.

striction is of vital importance in establishing successful thrombus formation in arteries. In general, the larger the area of bleeding, the larger the vessel involved. For example, pinpoint petechial hemorrhage develops from arterioles and venules, whereas large, ill-defined soft tissue bleeding (ecchymoses) occurs from veins, and rapidly expanding "blowout" hemorrhage results from arteries.

2
PLATELETS

STRUCTURE

Platelets circulate as anuclear, cytoplasmic disks with an average diameter of 3 to 4 μm and volume of 10 fl. Platelet size distribution is very broad compared with other blood cells. In the nonstimulated state the discoid shape is maintained by a circumferential cytoskeleton of microtubules (Fig. 3).

Membrane glycoprotein receptors mediate the surface contact reactions of stickiness, shape change, adhesion, internal contraction, and aggregation. Contact activation of the membrane phospholipids also generates procoagulant activity and arachidonic acid (see Fig. 2, Chapter 1). The surface membrane is continuous with a sponge-like, open canalicular membrane system, and interdigitates with the dense tubular system that is not surface-connected. Channels of the open canalicular system and dense tubular system in platelets form interwoven membrane complexes morphologically identical to the association of transverse tubules and sarcotubules in embryonic muscle cells. This dual membrane system appears to constitute the calcium-regulating mechanism. Submembranous filaments and cytoplasmic filaments of the sol-gel zone constitute the contractile system of the platelet. Platelets contain substantial quantities of muscle proteins, including actin, myosin, tropomyosin, α-actinin, actin-binding protein, filamin, and troponin.[14]