the HEMORRHAGIC DISORDERS

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A Clinical and Therapeutic Approach

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Introduction

THE need for another book on the hemorrhagic disorders might legitimately be questioned, since a number of excellent treatises are presently available. Our thought in writing the present volume, however, is that the needs of the practicing physician in his quest for useful information in this field have not yet been fully met. We have been particularly impressed with the great and possibly undue emphasis placed upon disorders of the coagulation mechanism, at times to the exclusion of other disturbances of the hemostatic mechanism. To be sure, the abnormalities of coagulation are of importance, and fascinating to boot. Nevertheless, they may be said to represent only one leg of a four-legged stool, of which the other "legs" are the vascular, the platelet and the fibrinolytic mechanisms. Thus, we have tried to utilize as broad an approach as possible, especially since a single defect as the sole cause of a given hemorrhagic disorder is unusual.

Essentially, this aims to be a practical book, based on the actual study of a very large number of cases of hemorrhagic disturbance. Our approach to these cases has been that of the clinician and the clinical investigator, with the laboratory studies representing only one phase of the management of the patient as a whole. Thus, details of therapy have been stressed throughout, a matter of particular importance to the practicing physician. In addition, a large number of didactic tables, diagrams and illustrations have been included, because we have learned to appreciate their value in teaching both the young medical student and his older counterpart, the graduate physician. They are, furthermore, instrumental in saving considerable space in the text.

In recent years a number of "new" entities have come to the fore, and it is of these, rather than of the better known disturbances such as hemophilia, that detailed descriptions have been made. Thus, the fibrinolytic purpuras, the hemorrhagic disturbances of pregnancy and the puerperium, the "dysproteinemic" purpuras, and the vascular purpuras are given the consideration which their relative novelty on the medical scene seems to require. One chapter is devoted to special therapeutic procedures useful in hemorrhagic disease, and an appendix presents a series of "screening tests" and other diagnostic procedures which will serve in the evaluation of most hemorrhagic disturbances.

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Particularly in this period, when the cost of investigation has reached peak levels, we are highly appreciative of the continued support to our research by the United States Public Health Service, National Institutes of Health; the Atomic Energy Commission; the American Heart Association; and the American Cancer Society. One of us (M. S.) was also supported by a Senior Research Fellowship of the National Institute of Health (1946–1949) and the Damon Runyon Foundation (1949–1952); and by an Established Investigatorship of the American Heart Association.

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Alphabetic List of Commonly Used Terms for Blood Coagulation Factors and the Denominations Used in This Text

Factor	Abbreviation	Definition in this monograph
Accelerin		Serum accelerator
Antihemophilic globulin[1]	AHG	Antihemophilic globulin
Antihemophilic globulin B	AHG-B	Plasma thromboplastin component[4]
Christmas factor		Plasma thromboplastin component[4]
Co-factor of thromboplastin		Labile factor[2]
Convertin (*see* Proconvertin)		
Co-thromboplastin		Stable factor[8]
Factor V		Labile factor[2]
Factor VII		Stable factor[8]
Factor VIII		Antihemophilic globulin[1]
Factor IX		Plasma thromboplastin component[4]
Labile factor[2]	LF	Labile factor
Plasma Ac-globulin		Labile factor[2]
Plasma prothrombin conversion factor	PPCF	Labile factor[2]
Plasma thromboplastin antecedent[3]	PTA	Same
Plasma thromboplastin component[4]	PTC	Same
Plasma thromboplastic factor A	PTF-A	Antihemophilic globulin[1]
Plasma thromboplastic factor B	PTF-B	Plasma thromboplastin component[4]
Plasma thromboplastic factor C	PTF-C	Plasma thromboplastin antecedent[3]
Platelet activator		Platelet thromboplastic factor[5]
Platelet thromboplastic factor[5]	PTF	Same

Alphabetic List—*Continued*

Factor	Abbreviation	Definition in this monograph
Precursor → serum prothrombin conversion accelerator	SPCA	Stable factor[8]
Proaccelerin		Labile factor[2]
Proconvertin → convertin		Stable factor[8]
Prothrombinase		Prothrombin converting complex[6]
Prothrombin converting complex[6]		Prothrombin converting complex
Serum accelerator[7]		Serum accelerator
Serum Ac-globulin		Serum accelerator[7]
Serum prothrombin conversion accelerator	SPCA	*see* Precursor → serum prothrombin conversion accelerator
Stable factor[8]	SF	Stable factor
Thromboplastinogen		Antihemophilic globulin[1]
Thromboplastinogenase		Platelet thromboplastic factor[5]

[1] Reacts with the platelet thromboplastic factor, plasma thromboplastin component, plasma thromboplastin antecedent and, possibly, other plasma factors to form plasma thromboplastin (see figure 11).

[2] Reacts with a complex of thromboplastin, stable factor and calcium to form the prothrombin converting complex (or prothrombinase). This, in turn, converts prothrombin to thrombin (see figure 12).

[3] Reacts with the platelet thromboplastic factor, antihemophilic globulin, plasma thromboplastin component and probably other plasma factors to form plasma thromboplastin (see figure 11).

[4] Reacts with the platelet thromboplastic factor, antihemophilic globulin, plasma thromboplastin antecedent and probably other plasma factors to form plasma thromboplastin (see figure 11).

[5] Reacts with several plasma factors (antihemophilic globulin, plasma thromboplastin component, plasma thromboplastin antecedent, possibly others) to form plasma thromboplastin (see figure 11).

[6] Formed by the interaction of thromboplastin, stable factor, calcium and labile factor. Converts prothrombin to thrombin, likely in the presence of calcium (see figure 12).

[7] Derived from the labile factor through the action of thrombin. In its presence, the formation of the prothrombin converting factor is accelerated (see figure 14).

[8] Reacts with thromboplastin and calcium to form a preliminary complex, which then reacts with the labile factor to form the prothrombin converting complex (see figure 12).

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The Normal Hemostatic Process

General Considerations

IT IS generally agreed that a normal hemostatic mechanism is a necessity for survival. The small repeated traumas of every-day life produce minor injuries to the blood vessels, leading to the ever-present danger of spontaneous hemorrhage. Extrinsic trauma by severing blood vessels results in bleeding that requires prompt control. The prevention of spontaneous bleeding and the control of traumatic hemorrhage require the perfect integration of a number of elementary mechanisms without which exsanguination might conceivably result from any injury however slight. Thus, the vascular wall must have normal resistance and contractibility. The platelets and the many factors which participate in the coagulation process must be normal not only in number or concentration but in their activity. It is certain that the very intricacies of these mechanisms afford many possibilities for insufficient hemostasis with resultant bleeding.

The relative importance of the various hemostatic mechanisms differs greatly from one species to another, and, in man also depends upon the size of the affected vessel. In the lower forms of life, the relatively simple functions of agglutination of platelets at the site of vascular injury, vasoconstriction, and the direct adhesion of the endothelial surfaces are mechanisms sufficient to control hemorrhage. However, when blood circulates within the vessels under positive pressure, as in mammals, these mechanisms may become inadequate. The formation of a solid clot of fibrin at the site of vascular injury may then represent an effective means of local tamponade. In man, the relative importance of platelet agglutination, endothelial adhesion, vasoconstriction and fibrin formation vary greatly in relation to the size of the injured vessel and the rate of blood flow in the area. Direct adhesion of the endothelial surfaces and local agglutination of platelets may be sufficient to insure efficient hemostasis following the injury of small venules and capillaries.[105] The control of severe hemorrhage from a large arterial vessel may fail, however, until the drop in blood pressure within the vessel, following serious loss of blood, permits the local accumulation of thrombin and fibrin. In such cases, hemostasis is greatly favored when a vessel lies against a hard

TABLE 1.—*The Physical Phases of Hemostasis Following Vascular Injury Arranged in Chronologic Order (A Hypothesis)**

(A) TEMPORARY HEMOSTASIS

1. Reflex, temporary, localized vasoconstriction (slowing of circulation within the vessel at the site of injury)
2. Agglutination of platelets
   - prolonged, generalized vasoconstriction (due to release of serotonin)
   - coagulation of blood
     - activation of thromboplastin
     - formation of thrombin
     - formation of fibrin
3. Retraction of the clot (perhaps also some lysis of the clot)

(B) PERMANENT HEMOSTASIS

4. "Organization" of the clot
5. Recanalization of the vessel and extension of a new endothelial lining.

* This hypothesis emphasizes the prominent role of platelets in the process of hemostasis. Platelets: (a) mechanically plug injured areas of the vessel; (b) supply a vasoconstrictor agent (serotonin); (c) help to initiate the process of blood coagulation by supplying a factor indispensable for the activation of thromboplastin; (d) supply accessory substances, each accelerating distinct phases of the blood coagulation process; (e) are indispensable for the retraction of the clot.

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surface (bone, ligaments, cartilage, etc.). The collection of blood outside the vessel compresses it against the hard, unyielding surface, which then acts as an efficient hemostatic agent.

The complexity of the hemostatic process can probably be illustrated best by reviewing briefly the sequence of events which follows the injury of small arteries and arterioles (the most frequently affected vessels) in the event of trauma (table 1). *Vasoconstriction*, limited to the area of injury and of temporary nature (fifteen to thirty seconds), quickly follows injury of the skin and vessels. Probably mediated through an "axonic reflex," its physiologic significance is rather obscure. Many investigators believe that the phase of vasoconstriction may enhance the later phases of the hemostatic process since the consequent reduction of speed of blood flow in the area might conceivably cause platelets to draw closer to the vessel wall and thus agglutinate more readily at the site of vascular injury. The next step, the *agglutination of platelets* in any area where the continuity of the vascular wall has been interrupted, may be considered the key mechanism of hemostasis.[615] Platelet deposition may, of course, mechanically plug areas where the continuity of the vessel has been lost. But of greater importance is the release of powerful "chemical" factors from platelets, following their agglutination and subsequent lysis. As this occurs, pronounced, generalized and persistent vasoconstriction sets in. Vessels, both injured and intact, local and distant, are effectively con-

tracted for as long as thirty minutes. This vasoconstriction appears to be due to the release by lysed platelets of serotonin (5-hydroxytryptamine), which is also found in the serum after completion of coagulation. Shortly thereafter fibrin threads become visible and a solid plug of fibrin is formed (*fibrin clot*). The fibrin clot soon begins to retract and, by approaching the wall of the vessel, may assure better control of bleeding. The *temporary phase* of hemostasis is thus completed. The clot is then partly digested and is later invaded by connective tissue (*organization*). The gap in the vessel wall is then permanently sealed off (*permanent hemostasis*) and from then on a slow process of recanalization of the vessel begins, which may take weeks or months. Finally, a new endothelium, proliferating from normal areas, invades and relines the vessel in its entirety.

This short description of the process of hemostasis suggests that normal hemostasis can occur only when the various mechanisms concerned are coordinated in optimal activity. Recognized today as important for normal hemostasis are the vascular mechanism, the platelets, the blood coagulation mechanism, and fibrinolysis. These various mechanisms, although quite distinct from each other, are very closely integrated, as is clearly revealed by studying the pathogenesis of bleeding in various types of hemorrhagic disorders. *Thus, a single abnormality of one of the hemostatic mechanisms may not result in bleeding, if all others are normal.* For example, patients with afibrinogenemia may have but little spontaneous bleeding, although it would be impossible to think of any more serious breakdown of the coagulation mechanism. As a corollary to the above statement, *severe spontaneous bleeding usually requires the involvement of more than one elementary hemostatic mechanism.* Thus, the severe mucosal bleeding of the acute variety of idiopathic thrombocytopenic purpura may be due not only to platelet deficiency but to a simultaneous abnormality of the small vessels. In parenchymal liver disease, not only is the concentration of the various coagulation factors reduced, but vascular resistance is decreased, while plasma antithrombin titer and fibrinolytic activity may be increased.[258, 638]

It should also be stated that therapeutic agents may affect more than one hemostatic mechanism simultaneously, a fact which again emphasizes their essential functional unity. A very interesting relationship, for example, exists between vitamin K deficiency and vascular fragility.[212, 638] In dicumarol intoxication, hypoprothrombinemia is accompanied by increased vascular fragility, and capillary bleeding is frequent. Both abnormalities are promptly corrected by the administration of vitamin K_1. Also in parenchymal liver disease, low plasma prothrombin activity and positivity of the tourniquet test are fairly well correlated, and both are corrected by the administration of large doses of vitamin K_1, provided