Hemorrhagic Diseases

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Preface

THE hemorrhagic diseases present a complex and trying problem in medicine, for they are often difficult to diagnose, troublesome to manage, and sometimes frustrating to treat. Because they are relatively uncommon, a physician usually has little opportunity from his own personal experience to become familiar with this group of diseases. As a consequence, when he encounters a bleeding state, he often has to seek information in the literature and more specifically in books devoted to this subject.

With the aim to supply the physician and the hospital laboratory with practical information in this field of medicine, I have written two monographs: one on the hemorrhagic diseases, the other on hemostasis. Since the publication of these monographs, such important new developments have taken place that a drastic revision has become necessary. It seemed advantageous to write almost a completely new book but to retain the historical material as a background for introducing the various aspects of hemostatic abnormalities and the well established hemorrhagic diseases.

It has been my good fortune to have begun my work in the field of hemorrhagic diseases a few years before the new and modern era had its birth. This afforded a unique opportunity to become well acquainted with the older concepts and to observe and follow the tremendous advances that were made in the present quarter of a century. During this period, I had the opportunity to see and to study nearly all the known types of hemorrhagic diseases, both in the laboratory and in the clinic. In writing this monograph, it has been my aim to present the subject of the hemorrhagic diseases in a practical and objective manner. I have drawn freely on my own experiences and findings as well as on those of other investigators. In the pursuance of the task, new tests had to be devised, existing procedures often had to be modified and standardized, newer approaches to therapy had to be explored, some widely accepted and plausible concepts had to be abandoned, and new theories and hypotheses had to be formulated to be used as guides, both for the interpretations of findings and for newer approaches to the study of defective hemostasis.

Since the confusion in blood clotting has not come nearly as much from the numerous theories as from the faulty laboratory methods—

and even more from bad technique—great emphasis has been placed on the need for the judicious choice of methods and the meticulous execution of each procedure, no matter how simple. In Part II, twenty-five tests have been outlined in detail. These are the procedures which are used by my associates and me, particularly for diagnosis and control of therapy.

In the organization of the book, each chapter has been made an independent unit, thus permitting its perusal without reference to previous or subsequent material. To attain this objective, a certain amount of repetition was inevitable.

In my studies of coagulation, I have had the stimulation and the assistance of a number of young men and women, both from this country and from abroad. I am particularly indebted to Miss Clara V. Hussey whose initiative, critical judgment, and technical skill have been great assets in the research program. I express my thanks to Miss Julita Snell who not only typed the manuscript, but also made many helpful suggestions and carefully checked the bibliography. The splendid co-operation I have received from my associates at Marquette University, Milwaukee Children's Hospital, and the Milwaukee Blood Center is deeply appreciated. The continuous financial support since 1946 by grants from the United States Public Health Service has made it possible to develop and maintain a research program devoted to the study of hemorrhagic diseases. I thank the various investigators who have permitted me to use their charts and other material, and the publishers, Lea & Febiger, for their patience during the many delays in the completion of my manuscript and for their many courtesies.

A.J.Q.

MILWAUKEE, WISCONSIN

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Part I. Clinical

Chapter 1

THE HISTORICAL DEVELOPMENT OF THE CONCEPTS OF HEMOSTASIS

IT is inborn in man to accept the bounties of nature and the contributions of his fellow men as a matter of course. To this the surgeon is no exception. Equipped with the tampon, the ligature and the hemostat, the surgeon so successfully achieves hemostasis that it rarely occurs to him that even such a simple tool as the ligature did not always exist. He probably does not know that it was perhaps first used by an unknown physician in the Alexandrian era, that it was forgotten for nearly a thousand years and then rediscovered by Ambroise Paré.

It is easy to overlook the fact that with every incision, innumerable capillaries, venules and arterioles are severed, because stanching occurs so automatically. It is not surprising, therefore, that the subject of hemostasis attracts relatively little attention, and that most modern standard textbooks of surgery barely mention this important physiological mechanism. Nevertheless, a function that is so perfected that it can cope both with the onslaught of man and the unfavorable environment resulting from disease makes it all the more worthy of intensive study.

VASCULAR CONTRACTION

No thorough understanding of hemostasis can be attained without a broad knowledge of its historical development. Until Harvey's monumental discovery of the circulation of the blood, all explanations of the control of hemorrhage were purely speculative. Petit[74] (1731) must be credited for the first scientific approach to the physiology of hemostasis. He concluded that hemorrhage is stopped by the formation of a coagulum of blood. He recognized that part of the clot was in the vessel and to this he gave the descriptive name bouchon (cork), and part was outside which he designated as couvercle (cover). He observed the adherence of clots to the internal coat of the vessel.

Five years later (1736) Morand[65] offered a second type of explanation. He postulated that an artery could undergo a longitudinal contraction resulting in corrugation or plaiting whereby the lumen was diminished. While Morand's hypothesis was anatomically faulty since the muscle fibers of arteries are circular and not longitudinal, he did introduce the important concept of contraction as a factor in hemostasis. With the annunciation of these two explanations for the control of hemorrhage, a controversy was initiated which remains unsettled even today. A number of the leading surgeons in England including Sharp,[90] Gooch,[27] Kirkland[47] and White[109] accepted the contraction theory in preference to Petit's hypothesis. It is interesting to recall that John Hunter[39] was particularly interested in traumatic arterial spasm and stated that an injured vessel has a natural disposition to contract. It remained for Jones[43] (1805) to present a concept of hemostasis which combined the divergent views, and disclosed a remarkable clarity of view. He stated: "We can no longer consider the suppression of hemorrhage as a simple or mechanical effect, but as a process performed by the concurrent and successive operations of many causes: these may be simply stated to consist in the retraction and contraction of the artery; the formation of a coagulum at its mouth; the inflammation and consolidation of its extremity by an effusion of coagulating lymph within its canal, between its tunic and in the cellular substance surrounding it."

In the nineteenth century especially during the latter half, the developments in the field of coagulation of the blood dominated and the contraction theory was either ignored or forgotten. The marked shift to Petit's original concept of hemostasis is illustrated by the fact that such eminent surgeons as Joseph Lister[56] not only upheld the coagulation theory, but contributed actively to its advancement.

In 1923 Magnus[60] again brought the contraction theory to the foreground. He showed that normal arteries on injury can contract so intensely that the lumen is obliterated and the flow of blood is completely stopped. He concluded that "the process of hemostasis must be considered more than heretofore as a property of the vessel itself and that the coagulation of blood is not the only, perhaps not even the essential factor in bringing about stanching." (Author's translation.) Interestingly enough Morawitz,[68] who in 1904 formulated the classical theory of coagulation, markedly broadened his concept of hemostasis twenty years later as evidenced by two of his statements:

"Blood coagulation is not the only factor which controls hemorrhage, yes, perhaps not even the most important."

"Thus, we see that for the control of bleeding one must regard blood and the vessel as interacting in an inseparable linked unity, and that

it is just as erroneous to attribute all anomalies (of hemostasis) to the blood as to consider only the vessel." (Author's translation.)

Similar views were expressed by Schulz,[89] Stich[97] and others. Küttner and Baruch[49] on the basis of the study of an extensive series of battlefield injuries emphasized segmental spasm of injured arteries, which they found was sometimes so intense that the severed free end of the vessel became pulseless. Stegemann,[93] although recognizing the importance of both contraction and coagulation, introduced and emphasized an additional factor in hemostasis, namely a shunting of the blood flow away from the site of injury. Tannenberg and Hermann[99] as well as others attacked this hypothesis. The clearest and no doubt final evaluation of shunting is given by Apitz[3] who stated: "The deflection of blood from an injured vessel is always the result; never the cause of stanching." (Author's translation.)

Tannenberg and Hermann were perhaps the first to emphasize clearly that purely mechanical factors may participate in hemostasis. According to Tannenberg and his students there is in addition to the physiological contraction, a retraction of the cut artery due to tension in and about the vessel and also the pressure exerted by the hematoma formed at the site of injury. Oddly enough this phase of hemostasis has received little attention. Recently, however, Tocantins[100] has critically and illuminatingly discussed these mechanical extravascular factors from the point of view of clinical application.

Even more important than the pressure or force that closes the vessel, is the consequence when intimal endothelial cells are pressed together. They develop a stickiness which results in a gluing action of sufficient strength to seal not only capillaries but even larger vessels. Stegemann[93] appears to have been the first to recognize the potentiality of this factor in the control of bleeding. He stated: "The strong contraction presses the intimal surfaces together for a considerable time and brings about a closure by adhesion." (Author's translation.) Herzog[32] concluded on the basis of studies on the capillaries of the frog's tongue that bleeding of capillaries is controlled in cold blooded animals primarily by adhesion. Roskam[85] postulated that this increased stickiness of irritated or injured endothelial cells is a type of opsonization brought about by the precipitation of an adhesive protein. Morawitz[68] also recognized the importance of this capillary adhesiveness in hemostasis and Apitz[3] recently again discussed this mechanism. He believed that it could be better explained on the basis of simple mechanical pressure, than by the more elaborate hypothesis of Roskam. Very recently Chen and Tsai[15] concluded that the capillary bleeding is controlled by adhesion of its walls as a consequence of endothelial injury. Chen and Tsai were

apparently not aware of the earlier work, for they state: "As the phenomenon of capillary adhesion after mechanical injury is so constant and persistent, it is difficult to explain why it has escaped the attention of previous workers." In a subsequent paper, they cite the observations of other investigators on capillary adhesions and add their own important finding that the adhesive force of the capillary of the toad may withstand a pressure of 200 mm. of mercury. The contraction of capillaries as a means of controlling hemorrhage remains difficult to evaluate. Chen and Tsai point out the complexity of the problem since capillary contractility varies according to species and situation. Macfarlane,[57] however, centers his concept of hemostasis on the vascular response to injury.

THE COAGULATION OF THE BLOOD—HISTORICAL HIGHLIGHTS

Experimental work on coagulation of the blood began three centuries ago and among the investigators are included the names of many illustrious men in medicine and in science. The development in this field may be divided into three periods: (1) the pre-classical theory era; (2) the classical theory era; and (3) the prothrombin era.

The Pre-Classical Theory Era (1666-1904).—The observation of Malpighi[61] in 1666 that strands of fibers remained after a clot of blood was washed can be regarded as the first attempt to gain an insight into the mysterious power of the blood to clot. A century later, Hewson[33] developed the first methods for keeping blood fluid outside of the body. He thereby laid the foundation for nearly all further study of coagulation. As a result of his investigation, it was established that the coagulation factors resided in the non-cellular moiety of the blood. Buchanan[12] in 1835 offered an explanation of the coagulation reaction which was based on laboratory studies. It anticipated some of the cardinal features of the classical theory. Buchanan compared the clotting of blood with the curdling of milk by rennin. In both, a ferment reacted with a soluble protein to produce a coagulum. Although Buchanan's work was apparently well-known in England, as evidenced by the fact that Lister[56] used his data as a basis for his own studies in 1863, it failed, nevertheless, to stimulate others and thus studies on coagulation declined in England, and a period of great activity began on the Continent. Hammarsten[29] (1877) contributed valuable information on fibrinogen, and was the first to state that only thrombin was necessary to coagulate this protein, while Schmidt[87] after many years of study formulated a logical scheme to explain the process of coagulation. He postulated that thrombin was