Bleeding Problems in Clinical Medicine

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PREFACE

Serendipity—the accidental discoveries to which much of man's progress in medicine can be traced—may be symbolized by the type of mold that drops into one's Petri dish, as was so dramatically illustrated during the life of Sir Alexander Fleming. In 1934 I had the good fortune to discover that the addition of a tissue extract to blood could make the clotting time more specific. From this evolved the one-stage prothrombin time. I had the further advantage of working with Dr. Frederic Bancroft, a scientifically minded surgeon through whose wide clinical contacts the method found prompt application. But even more propitious, the test became available at the same time vitamin K was discovered and while a mysterious bleeding disease in cattle was being traced to a toxic principle in spoiled sweet clover hay, which was eventually isolated and introduced into therapy to combat intravascular clotting.

Although the prothrombin time encountered some of the obstacles that most innovations do, nevertheless within 20 years it elicited comments such as: "In 1935 A. J. Quick presented his one-stage method of prothrombin in blood. At that time it could not have been foreseen that in doing this, he opened a new era in blood coagulation research." One might question that one simple test could open a new era. Perhaps it would be more accurate to state that the time was ripe for a renaissance in hemostasis and that the one-stage method was but one of the sparks to help set it off.

Since its inception, the prothrombin time has remained a valuable diagnostic tool and, in conjunction with the prothrombin consumption time, most coagulation defects can be successfully screened and identified. It has therefore been possible to study diagnostically nearly any bleeding state arising from a coagulation or a platelet defect. Difficulty continued, however, in establishing a diagnosis of a bleeding disease in which the basic defect is vascular. The only means for study in these cases were Duke's bleeding time and the tourniquet test, but these had

remained unstandardized and precarious to interpret. The observation that the Duke bleeding time is prolonged even in many normal subjects after ingesting aspirin, and significantly prolonged in patients with the Minot-von Willebrand syndrome, led to the development of the aspirin tolerance test, a promising new diagnostic tool.

For nearly four decades I have studied bleeding conditions both in the laboratory and at the bedside. These studies gave me the opportunity to discover several rare bleeding states of genetic origin and provided a source of key information concerning the mechanism of hemostasis. From this has developed the concept that hemostasis is the resultant of an evolutionary process. On this basis have the bleeding problems in clinical medicine been approached, classified, and illustrated with appropriate case presentations.

Grateful recognition is accorded to those who, through the years, assisted me in my research. Their contributions have been both valuable and stimulating. Particularly helpful has been the financial support from grants of the United States Public Health Service since 1946. To Terri Snell, especially, I express my sincerest appreciation and thanks for her capable and unstinting efforts to help bring this undertaking to completion.

ARMAND J. QUICK

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Chapter 1

The Story of Hemostasis

"Science begins with naive often mystic concepts of its problems. It reaches its goal whenever it can replace its early guessing by veritable hypotheses and predictable results."

THOMAS HUNT MORGAN

Hemostasis came into being eons ago with the first cardiovascular system, but man had little realization of its existence until the past few centuries. Bleeding, like pain, was an early heritage. Often it was self-inflicted. With the coming of the sword, the incidence of bleeding sharply increased and, even today, shows no signs of abatement. Hemorrhage as a complication of disease was slow in winning recognition. Terms such as "black smallpox" were ominous but gained meaning only when translated into hemorrhagic smallpox.

THE CONCEPTS OF HEMOSTASIS

No real understanding of hemostasis was possible until Harvey discovered the circulation of the blood. It required a century more before Petit[27] made the first attempt to explain stanching by postulating that hemorrhage was stopped by a coagulum of blood. An alternative mechanism, namely, vascular contraction, was proposed five years later by Morand,[23] but it never progressed much beyond the stage of speculation. To understand vascular participation in hemostasis requires considerable knowledge concerning microcirculation, which is only now coming into its own. Yet Malpighi's discovery of the capillaries marked the beginning of man's awareness of this vital system. Because of these discoveries, the names of Harvey and Malpighi will be forever linked, since "Harvey made their existence a logical necessity; Malpighi made it a histological certainty," as Fraser-Harris[9] once said. To the Italian master goes also the credit for the first con-

crete evidence of coagulation: the isolation of strands of white fibers from washing a mass of clotted blood. Nevertheless it took another 100 years before Hewson[15] demonstrated that these fibers separated out during the clotting of blood, but not until 1859 was the precursor of these strands isolated in a crude state by Denis[7] who named it plasmine, now called fibrinogen.

BLOOD COAGULATION. That a blood clot could serve as a hemostatic plug seemed so obvious that hemostasis soon became regarded as being wholly dependent on blood coagulation. The finding that the clotting time is prolonged in hemophilia added further support. It seemed logical to account for the bleeding on the basis of coagulation so slow that it did not permit formation of an effective fibrin plug.

Expectation that the problem of hemorrhage could be solved by finding an adequate explanation for blood coagulation attracted many noted scientists and clinicians to this field. The first question that naturally arose was: How is fibrinogen converted to fibrin? The credit for the correct answer belongs to Buchanan[5] who, in 1835, proposed the ferment theory, on the assumption that the process resembled the coagulating action of rennin on the proteins of milk. The ferment theory of blood clotting soon won recognition and the agent was named thrombin. Since it obviously could not exist in its active form in circulating blood, an inactive precursor, which eventually became known as prothrombin, had to be postulated. How this agent is converted to active thrombin engaged the interest and efforts of many prominent scientists of the latter part of the nineteenth century and, even today, continues to challenge workers in the field. The studies of Schmidt[34] suggested that an additional agent, which he named the zymoplastic substance, is needed, and the work of Arthus and Pagès[1] established that calcium is also essential in this conversion.

In 1904 Morawitz,[24] as well as Fuld and Spiro,[10] summarized the existing knowledge and formulated what is now the classic theory of coagulation. It consisted of two steps: (1) the action of calcium and the zymoplastic substance, now called thromboplastin, to activate prothrombin to thrombin, and (2) the action of thrombin on fibrinogen which then converted it to fibrin—the matrix of the clot.

All of this was achieved with practically only one laboratory test—the clotting time—which was both crude and unstandardized. It is easy to understand why the one-stage prothrombin time,[31] introduced exactly a century after Buchanan's paper,

supplied a new impetus. For the first time, a simple quantitative procedure was available to differentiate hemophilia from hypoprothrombinemia and to solve the cause of hemorrhagic states such as cholemic bleeding and the hemorrhagic disease of the newborn.

PLATELETS. Recognition of platelets as a factor in hemostasis came about indirectly through an extremely common condition called purpura. It was so closely associated with the pestilential fevers that many epidemic diseases were regarded as synonymous with purpuric fever. But in 1557 Amatus Lusitanus[20] reported a case of purpura without fever and, in 1734, Hornung[16] classified the purpuras into the simplex, the febrile, and the scorbutic. It is fairly certain that his astute classification was based more on intuition than on actual knowledge.

Platelets and purpura remained entirely unassociated, until Krauss[17] in his Inaugural Dissertation (1883) mentioned that his chief, Dr. Brohme, noted a marked decrease of hematoblasts or platelets in cases of purpura haemorrhagica in children. However, it was in the French school, especially under the influence of Hayem,[13] that the relationship of platelets to purpura was firmly established.

But the correlation of coagulation with platelets posed a problem, difficult and controversial even today. Both Bizzozero[4] and Hayem[12] presented evidence that platelets participate in the early phase of coagulation, for they observed that fibrin strands appear at the locus where platelets adhere and undergo morphological changes. They concluded correctly that platelets supply a factor needed in the clotting reaction. Nevertheless, the observation that the clotting time remains normal even in severe thrombocytopenia led many others to conclude that platelets are not necessary in the coagulation of blood. What supplied the answer to the role of platelets in coagulation was a test developed in 1947 called the prothrombin consumption time.[29] This procedure showed that even when the clotting time is normal, the prothrombin consumed is almost nil when normal plasma depleted of platelets by high centrifugation is clotted. The finding that platelet-rich hemophilic plasma also has very poor prothrombin consumption but that mixing platelet-rich hemophilic plasma with the platelet-poor normal plasma results in both a mutual correction and good prothrombin consumption clearly demonstrated that platelets do not contain a holothromboplastin. Rather, a clotting principle, now known to be a phospholipid, reacts with a plasma factor, which is lacking in hemophilia, to form thromboplastin.

HEMORRHAGIC DISEASES. Man's groping through the intricacies of hemostasis can best be chronicled by the manner in which he gradually came to recognize the existence of bleeding diseases and how he then developed means to identify and treat such states. Until very recently, infection dominated as a cause of bleeding. As already stated, in the Middle Ages the term "purpuric fever" encompassed such common diseases as smallpox and diphtheria, both of which were endemic and epidemic. In these and numerous other infectious diseases, thrombocytopenia was a common but often undetected underlying cause of the hemorrhagic complication. One should remember that in pulmonary tuberculosis hemoptysis not only often killed by a massive terminal hemorrhage but also induced a severe anemia that undermined resistance. In syphilis, rupture of an aortic aneurysm was a dramatic hemorrhagic complication. With the conquest of infection, many of the problems of hemostasis were unwittingly solved without, however, furnishing much basic information on how infection affects the platelets or coagulation or even vascular contraction.

Malnutrition is equally as important as infection in bringing about hemorrhagic complications. The most outstanding example of a nutritional disease that kills by hemorrhage is scurvy. How this occurs is still not clearly understood, but it is the consensus that an anatomical breakdown of mesenchymal tissue involving the microcirculatory system is caused by a lack of ascorbic acid. That such bleeding occurs despite normal coagulation and well-functioning platelets has not yet been sufficiently recognized to be fully integrated into a comprehensive scheme of hemostasis. How slow the recognition of nutrition as a factor in hemorrhage has been is strikingly illustrated by the recentness of the discovery of vitamin K. How many newborn infants died and still die of vitamin K deficiency, in regions of the world where malnutrition is prevalent, is difficult to estimate, but the serious bleeding that was often encountered postoperatively in the patient with obstructive jaundice was, as if by magic, wiped out almost immediately after vitamin K was discovered. While the practical aspects of vitamin K are established, its true physiological role remains unsolved. Likewise, the relationship of bleeding to immunological processes is only vaguely understood. One type of thrombocytopenic purpura which presumably is immunological in origin is designated idiopathic, thus disguising ignorance with a pretentious adjective. How hormones fit into the hemostatic mechanism is still almost entirely speculative.

In the acquired bleeding states the impairment of hemostasis

is usually complex, involving several components. Thus, in vitamin K deficiency at least four clotting factors are depressed, thereby making it exceedingly difficult to correlate the clinical picture with the laboratory findings.

The recognition of the existence of hereditary bleeding diseases marked an important step forward in man's unraveling of the enigma of hemostasis. To Otto[26] should go the honor of establishing the first hereditary hemorrhagic disorder. Fortunately, it was not called Otto's disease. Although the name hemophilia can hardly be regarded as an erudite combination of Greek terms, it is at least euphonious. For nearly a century after hemophilia was established as a clinical entity, no significant contributions to the actual knowledge of the mechanism of hemostasis were made. The recognition gained by other hereditary states, such as hereditary telangiectasia,[33] congenital afibrinogenemia,[32] and a nonthrombocytopenic purpuric state reported in 1920 by Minot and Lee[22] and a little later by von Willebrand,[36] also failed to advance significantly the basic concepts of hemostasis.

The actual utilization of the hereditary hemorrhagic diseases as a means for solving the mechanisms of hemostasis came after 1935. The finding that hemophilia is caused by the lack of a single clotting agent—factor VIII—led to the discovery of other hereditary bleeding diseases in which a single specific factor is missing. Over 15 such genetically-induced diseases are now available with which to probe the mechanism that protects against loss of blood.

HEMOSTASIS IN SURGERY. Lack of knowledge concerning hemostasis was not a deterrent in surgery since bleeding in the normal subject could be controlled by the tampon, ligature, and hemostat. After the introduction of blood transfusions, it was possible to replace lost blood, thereby preventing exsanguination. Often, unknowingly, the transfusion supplied hemostatic factors that were depleted or lacking. It was only after the introduction of vitamin K into the treatment of the jaundiced patient that the subject of hemostasis elicited a renewed interest in surgery.

HEMOSTASIS AS IT PROBABLY EVOLVED IN NATURE

All life processes are a product of evolution, but hemostasis is an exceptionally propitious example for illustrating a multifaceted physiological mechanism with indeterminable ramifica-

tions, yet retaining a fair degree of unity and simplicity for tracing the steps in its development. Just as the anthropologist and paleontologist find valuable clues in fossils to aid them in explaining evolution in structure, so the hemostatic processes in existing species of life serve as a veritable storehouse of information for constructing the probable course of functional evolution.

In the primitive species the hemostatic requirements are contained solely in the vascular system. Thus, in the larva of the honey bee no distinct coagulation occurs.[3] "Apparently, the viscosity of the blood which is characteristically high in some insects is an important factor in preventing undue bleeding, and even more important, the blood pressure, as Mellanby[21] has pointed out in these lower forms of life, is below atmospheric pressure. Consequently, little blood can be lost. Some insects, it might be remarked, employ reflex bleeding (extruding a distasteful blood) to repulse their predator."[28] Because of the minuteness of these organisms, hemostatic studies are difficult and unsatisfactory, hence the lack of available information. Yet it is apparent that vascular control is present even in the most primitive organisms.

As more complex species evolved, the blood pressure increased and the need for more efficient stanching arose. This was met in part by stronger and thicker-walled blood vessels, but, in addition, there appeared in the blood a cell endowed with the property of agglutination, thereby forming a coagulum that could serve as a mechanical plug for sealing injured vessels. The most extensively studied cell of this type is the amebocyte found in the blood of the *Limulus*. According to Loeb,[19] when *Limulus* blood comes in contact with a foreign surface, the amebocytes begin to adhere and agglutination occurs. The cells undergo marked change, pseudopodia appear, and a syncytial coalescence results; Yeager, Shull, and Farrar[37] reported a similar type of mechanism in the cockroach. They state that "the cells lose their original fusiform or discoid shapes, round up, become more refractive, form thread pseudopodia, agglutinate into clumps, spread out and seemingly disintegrate."

Thus it appears that hemostasis can be achieved by cellular means in addition to vascular contraction with no participation of the plasma and that gradually in the process of evolution extracellular activity appears. This is difficult to trace but, interestingly, in Hardy's studies[11] of the explosive corpuscles in the blood of the *Astacus*, a coagulable protein—probably a primitive fibrin—appears. It is likely that in cells such as the amebocyte, a

reaction similar to blood clotting occurs for, as Levin and Bang[18] suggest, "the amoebocyte may contain the cellular counterpart of mammalian fibrinogen."

It may be postulated that blood coagulation did not originate independently in the plasma but came about through a transfer of certain intracellular clotting factors to an extracellular status. In this dichotomy, the platelets of mammalian blood and the thrombocytes of amphibian and avian blood resulted. The platelets and thrombocytes may be regarded as descendants of the amebocytic type of cell in which the clotting phase has been transferred extracellularly. But the intimate functional relationship between the clotting mechanism of the plasma and the cellular elements is not completely lost. Plasma scrupulously freed of platelets or thrombocytes fails to clot. Likewise platelets carefully washed to remove all traces of plasma lose their tendency to agglutinate, or become sticky, and no longer exhibit viscous metamorphosis. Obviously coagulation requires both the plasma and the platelets, and the agglutinating action of platelets is basically influenced by the coagulation mechanism.

Of special interest is the relationship of the erythrocyte to the thrombocyte and platelet. In the frog the erythrocyte and the thrombocyte are fairly similar in morphology. Both are nucleated and both can agglutinate in a rather characteristic rosette pattern. Although it is the thrombocyte which supplies the specific clotting factor needed for the generation of intrinsic thromboplastin, it would be interesting to know whether the frog erythrocyte can also supply this factor. This question is germane since the human erythrocyte actually has a higher concentration of the specific phospholipid, which I have named erythrocytin,[30] than the platelet itself. It remains inert only because the erythrocyte stays intact. Whether the high content of erythrocytin has any hemostatic function has not been investigated. It seems certain, however, that massive hemolysis, in which erythrocytin is liberated in large amounts, accounts for some of the untoward effects such as those that occur during a sickle cell crisis. That a relationship exists between the erythrocytes and the platelets is also indicated by the observation that in severe pernicious anemia, the maturation and production of both erythrocytes and platelets are depressed. It is very probable that the phylogenic link between erythrocytes, thrombocytes, and platelets is worthy of study.

EVOLUTIONARY SEQUENCES. One facet of evolution to be kept in mind is that new processes do not abruptly replace the

established mechanisms but are superimposed upon them. While the new dominates, the vestigial influence of the earlier mechanism may still remain, even though greatly curtailed and modified. This is clearly illustrated in the genesis of hemostasis. The first and most primitive response to vascular damage is contraction. During the contractile phase, platelet adherence to an injured vessel wall occurs, and the formation of a platelet thrombus and localized blood coagulation bring about effective closure of the injured vessel. Three basic but overlapping steps are involved: the vascular, the cellular, and the plasmatic. The third step is the last that evolved and phylogenetically the most recent. But in the parlance of evolution, the term "recent" bears the same relation to the commonly accepted meaning as "light year" does to "year." Thus, the fish, frog, and turtle already have a coagulation mechanism remarkably similar to that of man, despite the enormous developmental gap. Yet man has retained the vascular mechanism that functioned before either blood coagulation or platelets existed. An attempt will therefore be made to evaluate and correlate the mechanisms underlying the three major sequential steps in hemostasis.

Vascular Phase. One can assume that the strength and thickness of the arterial vessel are mainly the resultants of the augmented blood pressure as the complexity of the organism increased. When an artery of even fairly small size is severed, the hemostatic mechanism is inadequate and mechanical ligation is often required to stop the bleeding. The veins with a low and even negative blood pressure rarely present a hemostatic problem. It is the microcirculation that is figuratively the Achilles heel. The arterioles are often in exposed positions, yet carry blood under pressure and have relatively thin walls. The capillaries themselves have little or no contractile power and the blood flowing through them is regulated by a precapillary arteriolar sphincter.[38] When this control is disturbed, the resulting dilation of capillaries may bring about diapedetic bleeding. Of particular importance, since it supplies mechanical support, is the connective tissue matrix in which the microcirculation is imbedded. The dependence of this tissue on adequate nutrition can be an important factor in hemostasis, as illustrated by the bleeding in scurvy.

Cellular Phase. The platelet having evolved from a multifunctional primitive cell retains certain properties of its progenitor. Although it no longer has a complete cell structure, it retains, for example, the glycolytic cycle with its chain of enzymes so that

it has the power to generate ATP. The establishment in the platelet of an actomyosin-like protein[2] and the discovery that ADP is a factor in platelet agglutination[14] help to unify two functions of platelets: clot retraction and agglutination. Equally well established is the participation of the platelets in blood coagulation. Without platelets, no intrinsic coagulation occurs because no thromboplastin is generated.

Even though these three functions of the platelets are based on sound experimental studies, they do not automatically supply the answer to the question of what the role of the platelet is in hemostasis. Does clot retraction function as a physiological ligature as Fonio[8] expressed it, or is it, as Budtz-Olsen[6] views the process, a "redundant phylogenetic relic of no value to the organism"? Should the same evaluation be given to platelet clumping? It seems certain that in man the platelet thrombus—the clou hémostatique—does not hold the essential role in stanching as does the agglutinated mass of amebocytes in the *Limulus,* but how much does platelet clumping contribute to stanching? If one were to judge the participation of platelets in blood coagulation by the clotting time, the conclusion would be that it is negligible, since the clotting time remains normal even when the platelet count is extremely low. But when clotting is gauged by the prothrombin consumption time, the close relationship of the platelets to coagulation is clearly demonstrated.

The platelet occupies a central position in hemostasis, for not only does it possess properties that affect hemostasis or perhaps even directly effect stanching, but it literally is the bridge or link between the purely vascular response and the coagulation mechanism. Its role in controlling bleeding in the microcirculation is clearly indicated by clinical observation but is still difficult to interpret. The participation of platelets in coagulation is readily demonstrable in the laboratory but just how this affects hemostasis remains to be determined.

Plasmatic Phase. The deeply ingrained concept that coagulation of the blood is the key step in hemostasis is probably quite inaccurate. Morawitz,[25] the astute student of coagulation, as early as 1926 remarked: "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 vessels as interacting in an inseparably linked unity and that it is just as erroneous to attribute all anomalies [of hemostasis] to the blood as to consider only the vessels."

The hypothesis that blood coagulation is a late development