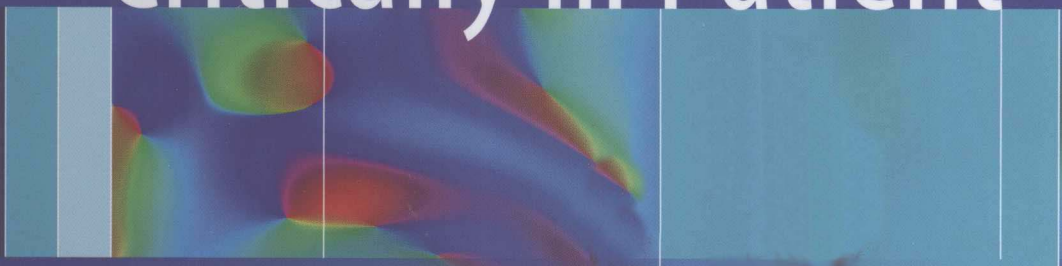
Hemocoagulative Problems in the Critically Ill Patient



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This book is dedicated to all those patients who I treated during my first 30 years in Intensive Care Medicine and to those I shall treat in the coming years. Each of them taught or will teach me something

Preface

Libraries contain plenty of textbooks and manuals that are dedicated to the care of the critically ill and cover all aspects of treatment, with a particular focus on mechanical ventilation, cardiovascular and renal support, nutrition, and infection control. However, location of a text devoted to blood coagulation is more difficult, which seems surprising when one considers the growing interest in the multiple interactions linking the blood coagulation system to the inflammatory response and the difficulties in identifying and treating blood coagulation disturbances in patients with multiple organ dysfunctions. While large books on critical care and anesthesia typically include a chapter on this issue, it will inevitably be embedded among dozens of other chapters or sections and is likely to be difficult to look up at the bedside. We therefore wanted to fill this gap by providing the reader with a handbook which is both up-to-date and easy to consult. Its preparation passed through a variety of phases. Initially, we considered which are the most frequent issues to arise regarding blood coagulation during daily clinical rounds in the intensive care unit. Subsequently, we asked colleagues interested in the field to prepare one or more chapters relating to these issues. The choice of authors was based on their clinical experience, as we are convinced that only physicians with a hands-on attitude are able to recognize the needs of readers involved daily in the care of critically ill patients and to select those aspects essential to clinical practice. Individual sections are dedicated to the physiology of blood coagulation, laboratory evaluation, inborn defects, and alterations acquired under different conditions specific to critical diseases and the perioperative period. In addition, however, we wished to include chapters addressing (relatively) rare diseases such as the vasculitides, either because of the life-threatening multiple organ dysfunction that they cause or because of the difficulties encountered in their recognition.

Like everything in this era of rapidly growing knowledge, this book is destined to undergo rapid aging: as an example, the sad end of the saga of recombinant human-activated protein C prompted us to rewrite the section dedicated to this

substance. Against this background, it will be up to readers to decide whether an updated edition of this text is needed in the next few years; should this be the case, we shall do our best to revise the text suitably and with the same enthusiasm and commitment that we have devoted to this book.

Trieste, March 2012 Giorgio Berlot

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Physiology of Hemostasis

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Paola Pradella, Federica Tomasella and Luca Mascaretti

1.1 A Brief History of Blood Coagulation

The unraveling of the mechanisms of one of the most remarkable characteristics of blood, its ability to clot, has taken almost one century.

The understanding of how coagulation works proceeded in a stepwise fashion as illustrated in Fig. 1.1, which shows some of the milestones in blood coagulation research. A considerable amount of basic work on protein chemistry and enzymology was conducted at the beginning of the last century in Europe and the USA. At that time, Morawitz described the conversion of prothrombin to thrombin by thrombokinase and the conversion of fibrinogen to fibrin by thrombin. In Morawitz's view, thrombokinase was derived from platelets and damaged tissue. A few years later, Howell coined the term "thromboplastin," by which he meant a complex with clotting-accelerating activity derived from tissue, with the ability to convert prothrombin to thrombin. The numerous studies on thromboplastin allowed the successive purification of tissue factor (TF) from human and bovine tissue.

One important discovery in enzymology was "limited proteolysis" [1], i.e., the breaking of specific peptide bonds depending on the amino acid sequence of a protein (as opposed to "unlimited proteolysis," which refers to the complete breakdown of a peptide to amino acids). Limited proteolysis is common to those complex biological systems based on highly regulated cascades, such as the complement system, apoptosis pathways, and blood coagulation.

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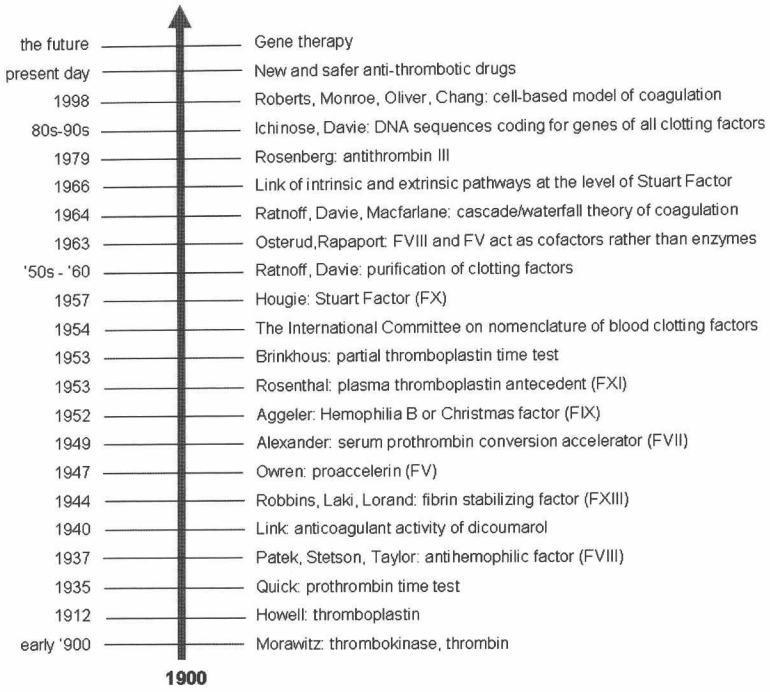

Fig. 1.1 Milestones in blood coagulation research

The understanding of blood coagulation in humans is closely linked to the study of patients with blood coagulation disorders. In the years from the mid-1930s to the end of the 1950s, almost all clotting factors were described (Fig. 1.1) and isolated using techniques such as column chromatography. As clotting factors were discovered, they were given names (sometimes more than one) in an unorganized manner, generating confusion; in 1954 the International Committee on Nomenclature of Blood Clotting Factors was established and has met several times since [2].

Given that a number of coagulation factors were described, the problem was to understand in which way they interacted to form the blood clot. What seemed to be relatively certain quite early on was that clotting factors were present in plasma as precursors (inactive form) and became activated by enzymes in a stepwise manner, probably by the mechanism of limited proteolysis. Another important observation was that calcium ions played a major role in the activation of some clotting factors.

At the beginning of the 1960s, the idea of an intrinsic as opposed to an extrinsic pathway of blood coagulation started to emerge; whereas the former can be initiated in a test tube, the latter needs tissue extracts to be triggered.

In 1964 two seminal articles were published, one in *Science* [3] and one in *Nature* [4]. Davie and Ratnoff [3] claimed the following: "A simple waterfall sequence is proposed to explain the function of the various protein clotting factors during the formation of the fibrin clot. When clotting is initiated, each clotting

factor except fibrinogen is converted to a form that has enzymatic activity. This activation occurs in a stepwise sequence with each newly formed enzyme reacting with its specific substrate, converting it to an active enzyme." It is interesting to note that the article by MacFarlane [4] used a term very similar to that employed by Davie and Ratnoff, "coagulation cascade."

So by the mid-1960s, a good model of blood coagulation was available. It was duly refined in successive years, mainly clarifying the role of Stuart factor (factor X, FX), which is the link between the intrinsic and extrinsic pathways. Other major advancements in coagulation were the recognition of the more prominent role played by the extrinsic rather than the intrinsic pathway in blood coagulation as a consequence of vascular injury, and that some coagulation factors (factor VIII, FVIII, and factor V, FV) acted as cofactors and did not display enzymatic activity.

In the 1970s, the plasma inhibitor antithrombin (AT) III was discovered and intensive research on regulatory pathways of coagulation allowed the identification of protein C and protein S.

The 1980s marked the beginning of the molecular era, with the cloning and sequencing of all the clotting factors. This was a very significant advancement in coagulation since it allowed mutations in clotting factors of patients with bleeding disorders to be determined. It also paved the way for the production of recombinant clotting factors for patients with hemorrhagic diseases.

In 1998, a novel coagulation theory was proposed by Roberts et al. [5], termed the cell-based model of coagulation. Currently, this is the accepted model and will be discussed at length in the following sections of this chapter.

1.2 Evolution of Blood Coagulation Systems

Comparative biology is a branch of biological science which applies a multidisciplinary approach to the study of biodiversity and complexity of biological systems, including coagulation.

One of the more primitive and well known coagulation systems is that of the horseshoe crab, or *Limulus*, an invertebrate of the Arthropoda phylum which has lived on Earth for more than 350 million years and is therefore also known as a living fossil [6]. These organisms have an open circulation and their blood (hemolymph) contains a protein called hemocyanin which transports oxygen. Amebocytes, also known as hemocytes, are the only circulating cells and have two main functions: that of killing pathogenic bacteria by means of bactericides and that of releasing coagulation zymogen proteins (proteases) which convert coagulogen (a clottable protein) to coagulin (a monomer), which in turn is polymerized by a transglutaminase. It is clear that this "ancient" and very basic coagulation system has many similarities to the more sophisticated coagulation systems of mammals.

The question that comparative biologists and coagulation experts asked themselves was why in vertebrates did the coagulation system evolve into such a complicated pathway composed of so many factors which, apparently, achieve the same result (blood clotting) as the more simple systems of invertebrates?

The reasonable explanation is that in *Limulus* the open circulation has a low pressure and the rather simple coagulation system suffices. On the other hand, vertebrates have high-pressure vascular systems and therefore evolution has "selected" a more sophisticated coagulation system able to produce localized clotting at the vascular injury level.

The availability of molecular biology tools such as degenerate PCR, reverse transcription techniques, cloning, and sequencing has allowed further insights into the evolution of coagulation systems of different species. Davidson et al. [7] investigated the coagulation systems of chickens (*Gallus gallus*) and the teleost puffer fish (*Fugu rubripes*); whereas the common ancestor of the former and humans dates to some 350 million years ago, the latter shared an ancestor with humans 430 million years ago. The authors were able to demonstrate that domains common to the proteases factor VII (FVII), factor IX (FIX), FX, and protein C (Gla-EGF1-EGF2-SP) and domains common to FV and FVIII (A1-A2-B-A3-C1-C2) were indeed present in both chicken and bony fish, proving that blood coagulation systems evolved over 430 million years ago.

1.3 Models of Coagulation: Cascade Versus Cell-Based

As mentioned previously, a "waterfall" or "cascade" model was proposed in 1964 [3, 4] and was subsequently refined, elucidating the identity and function of the single procoagulant proteins in a sequential series of proteolytic reactions. Each clotting factor is believed to be a proenzyme that cleaves and activates the next in the series, leading to a burst of thrombin generation. Successively, this model was corrected with the observation that some procoagulant molecules are cofactors and do not possess proteolytic activity. It is recognized that thrombin and other coagulation factors are serine proteases and that their activity requires calcium, phosphatidylserine, and other anionic phospholipids. The coagulation process is depicted as a Y-shaped scheme, with factor XII and FVII initiating, respectively, "intrinsic" and "extrinsic" pathways, merging at the level of activated FX (FXa)/activated FV (FVa) (prothrombinase complex) on a "common" pathway (Fig. 1.2). The intrinsic pathway is triggered by a negatively charged surface (contact phase) and all the components are present in blood, whereas the extrinsic pathway, primed by a trauma in a vessel wall, requires TF, a protein mostly present on subendothelial cells, as described in the specific section. In this model, coagulation factors direct and control the overall process and cells merely provide a surface containing phospholipids, on which procoagulant complexes are assembled.

Eventually this model was found to be inconsistent with some clinical observations, for example the TF/activated FVII (FVIIa)-initiated activation of FX cannot compensate for FVIII or FIX deficiency in hemophiliacs, and the reduction of single coagulation factors, mostly of the intrinsic pathway, is associated with different risks of hemorrhage. Subsequently, the hypothesis that intrinsic and extrinsic pathways are linked in vivo and the TF/FVIIa complex is the major initiator of hemostasis was proposed, as a consequence of the observation

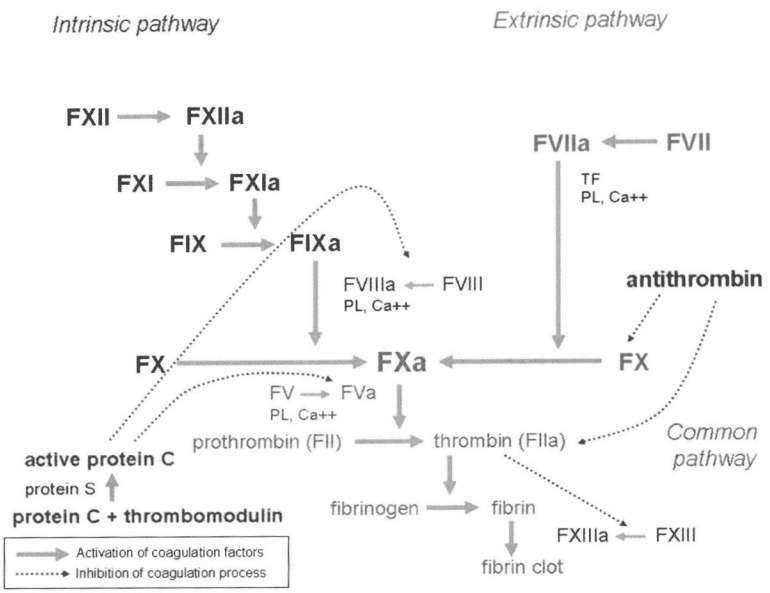

Fig. 1.2 The waterfall or cascade model of coagulation

that TF/FVIIa can activate FIX as well as FX, and thrombin is a physiologic "activator" of factor XI (FXI) on activated platelets. Moreover, in the last decades different receptors for many components of hemostasis and procoagulant or anticoagulant proteins on different cells have been detected, thus suggesting that cell surfaces have a central role in the coagulation process. Therefore, at the end of the 1990s, a cell-based model of coagulation was proposed, consisting of three stepwise and partially overlapping phases [5, 8]:

1. Initiation of coagulation on TF-bearing cells, during which FX and FIX are activated and a small amount of thrombin is produced to promote the coagulation process and platelet activation.
2. Amplification of the response, which implies that coagulation is shifted from TF-bearing cells to the nearby platelets; platelets adhere to subendothelial structures, undergo activation, and collect activated proteins on their membranes. The fact that the TF/FVIIa complex is close to activated platelets represents a crucial step for priming the hemostatic process or thrombosis.
3. Propagation phase, when platelets are recruited to the site of injury, and activated coagulation factors meet their cofactors to compose the procoagulant complexes necessary for the burst of thrombin generation and the fibrin polymerization.

In this model the extrinsic and intrinsic pathways are viewed as not independent. The role of the cell-based extrinsic pathway is to generate, on the TF-bearing cells, the small amount of thrombin needed to initiate and amplify the coagulation process, and that of the cell-based intrinsic pathway is to produce, on the platelet