ANALYTICAL REVIEW

Factor VII (SPCA)

Its Physiopathologic Significance

By Pietro de Nicola, M.D.

EARLY IN 1951 the position of the new clotting factors in the blood coagulation mechanism was critically reviewed in this journal.[1] At that time some factors could not be taken into consideration and analyzed because the data available were not yet sufficient for their adequate characterization. In May 1952 it was already possible to establish definite groups of new clotting factors and to suggest their equivalence,[2] as had been already tentatively presented in the previous months.[3, 4]

The purpose of this review is to focus attention upon only one group of these new clotting factors, a group that has been extensively studied during the last four years by various investigators. The factors included in this group are called by various names, such as serum prothrombin conversion accelerator (SPCA),[5] co-thromboplastin,[6] proconvertin-convertin,[7] factor VII,[8] and other terms which will be mentioned in the course of the review.

Historical Development

The historical development of this new group of clotting factors can be outlined as follows: After the discovery of the first group of new clotting factors,* it was soon realized that some other factor was important for the conversion of prothrombin into thrombin. The early investigations of Mann and associates,[16] Owen and Bollman,[17] and MacMillan[18] dealt with the coagulation defect induced by Dicumarol and postulated that such a compound could cause a decrease not only of prothrombin but of an additional factor as well. The other group of factors was not considered, since no variations of them were detected during the Dicumarol treatment.[19, 20]

The first complete observations were published in 1949, when SPCA was described by Alexander and associates[5] and its behaviour characterized in various physiopathologic conditions. Co-thromboplastin was the name suggested by Mann[6] for a factor which was believed to require the presence of thrombo-

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* Labile factor,[9] factors V and VI,[10] globulin of Fantl and Nance,[11] plasma and serum Ac-globulin,[12] plasmatic cofactor of thromboplastin,[13] plasma prothrombin conversion factor(PPCF),[14] proaccelerin and accelerin[15]: these factors are here referred to as Ac-globulin or labile factor.

plastin for its activity, and which decreased during Dicumarol treatment. Possibly the same group of factors are referred to by Jacox[21] (prothrombin conversion factor: PCF), by Quick and Stefanini[22] (prothrombinogen), and by the author.[23]

Proconvertin-convertin were then described by Owren,[7, 32] who had already made some preliminary remarks about their existence in 1947 (co-factor V)[10] and in 1949.[24] In 1951 Koller and his associates[8] suggested the term factor VII for the new group of clotting factors, and described in detail a simple technic for the supposedly quantitative measurement of factor VII. We have adopted the term factor VII for use in this review, as our experiments were based on Koller's technics.

General Characteristics

One of the most positive characteristics of factor VII is its stability, as opposed to the lability of the other group. This characteristic suggested the term "stable

Table 1.—*Adsorption and Elution of Factor VII and Allied Factors*

	SPCA	Convertin	Factor VII	Co-thrombo-plastin	Prothrombi-nogen
Adsorption on					
Barium sulphate	+	+	+		
Barium carbonate	+	+			
Tricalcium phosphate			+	+	+
Elution by					
Sodium citrate	+	+	+	+	+

factor"[25, 26] for factor VII and allied factors, to simplify the terminology of papers on blood coagulation. The activity of factor VII, as measured by Koller's technic, remains unaltered in serum kept for four days between 25 and 37 C.[8] As prothrombin and Ac-globulin or labile factor disappear very rapidly in serum, it is possible to obtain in this way a serum which contains high amounts of factor VII but is depleted of the other two factors. Also in dry plasma or serum the activity of factor VII, as measured in terms of SPCA, remains practically unaltered.[27]

Work carried out by means of the adsorption and elution technic showed significant characteristics of factor VII and allied factors, which are summarized in table 1.

Factor VII preparations are obtained from serum, practically free of prothrombin and labile factor (Ac-globulin), by means of adsorption on barium sulphate and elution with sodium citrate. For SPCA preparations a further purification by means of ammonium sulphate was suggested.[28] The adsorption and elution technic yielded relatively purified preparations of factor VII and SPCA. The electrophoretic patterns of factor VII show the presence of two major components.[29] The adsorption in the ultraviolet of SPCA preparations presents a typical curve.[27]

The authors who suggested such technics were able to obtain these factors

from serum. Alexander noted difficulty in obtaining the plasmatic precursor of SPCA, since this rapidly evolves to the active form of SPCA, while Koller and associates mentioned the possibility of obtaining factor VII from plasma.[30]

Another typical pattern of factor VII is its behaviour during Seitz filtration. By twice filtering bovine plasma through filters containing 20 and 30 per cent asbestos, respectively, practically all of factor VII is retained by the filters. In the filtrate there is still a small amount of prothrombin (about 15 per cent[8]), while Ac-globulin (labile factor) and fibrinogen are only slightly decreased. If the filtration is carried out through 50 per cent asbestos filters, all factor VII and prothrombin are presumed to disappear from the filtrate. Such data have been presented in terms of values obtained before and after filtration. No attempt has been made to further characterize the mechanism of Seitz filtration, which should involve the knowledge of physicochemical fundamentals.

On the basis of these results, "quantitative" methods for the measurement of factor VII activity or factor VII + prothrombin activity were suggested. They are modifications of the original one-stage method for prothrombin: all factors are kept constant, except the factors to be measured. For factor VII analysis, a substrate containing constant amounts of prothrombin, fibrinogen, and Ac-globulin (labile factor) are used. If the combined activity or factor VII + prothrombin is to be measured, the substrate will contain only fibrinogen and Ac-globulin (labile factor). Optimal amounts of calcium and an excess of thromboplastin are employed in all these experiments.[30]

Mechanism of Factor VII Activity

There is general agreement that factor VII and allied factors are implied in the early stages of prothrombin conversion. It is still debatable whether: (a) a precursor is necessary and/or detectable by means of the present technics; (b) factor VII or allied factors enter in the coagulation mechanism earlier than factors of the other group (labile factor, Ac-globulin) and require the presence of thromboplastin for their activation; (c) they actually accelerate the blood coagulation.

As to the first point, Alexander and associates admit the existence of a plasmatic precursor of SPCA, although they could not measure it quantitatively.[31] Owren believes in the existence of both a precursor and an active form (proconvertin-convertin) and to the possibility of measuring them separately.[32] Koller was not able to confirm this in terms of his technics. Other factors, which are supposed to be similar to factor VII, were not described as related to inactive precursors.

The problem as to whether factor VII and allied factors act earlier than others is still unsettled. According to the majority of authors, it is not yet possible to answer this question. Owren admits, however, that the active form of thromboplastin, as resulting from the interaction of a plasma and a platelet factor, is necessary for the activation of proconvertin to convertin. Only active convertin should be able to react with the other factors in prothrombin conversion.[33]

Several difficulties are encountered in interpreting the actual mechanism of factor VII and allied factors in blood coagulation, namely whether they are to be considered as accelerators or as conversion factors. When the position of

such factors was not yet completely clarified, Stefanini[1] had used the term "conversion factors" for the group referred to as labile factor or plasma Ac-globulin, etc. On the other hand, the term "accelerators" was given to serum Ac-globulin, factor VI, PCF, and eventually SPCA. The serum accelerating activity described by Stefanini was assigned the same properties. This author assumed that the serum accelerator described by Bordet was probably similar to factor VI or serum Ac-globulin. It was also suggested that such an accelerator should be considered by evaluating both serum Ac-globulin or factor VI and

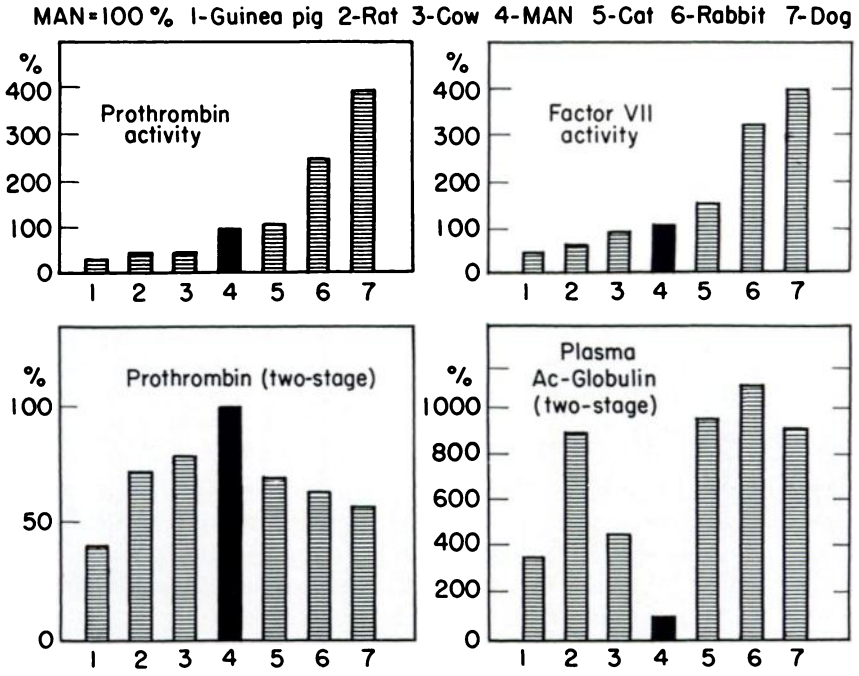

FIG. 1.—Factor VII, prothrombin (one-stage), prothrombin (two-stage), Ac-globulin (two-stage) determinations in various mammals: correlation between factor VII and prothrombin (one-stage) values; no correlation between prothrombin (one-stage) and prothrombin (two-stage) or Ac-globulin (two-stage). Technical details have been given previously.[36]

Man = 100%; 1—guinea pig; 2—rat; 3—cow; 4—man; 5—cat; 6—rabbit; 7—dog.

SPCA, in connection with their accelerating properties. This is probably true also for factor VII and allied factors. Other authors are of the opinion that Ac-globulin or proaccelerin-accelerin are the real accelerators, and proconvertin-convertin merely a conversion factor.[12, 33]

Research conducted in 1952 on the behaviour of the various clotting factors in several species allowed us to give some explanation to this problem. Prothrombin and factor VII activity were measured by means of the one-stage method, and the results compared with quantitative prothrombin and Ac-globulin analysis, as measured by the two-stage method. It was observed that a definite correlation existed between the prothrombin time and factor VII activity in the various species taken into consideration. On the other hand, no correlation could be detected between these two patterns and the prothrombin

and Ac-globulin concentration (fig. 1).[36] Even in the presence of high amounts of Ac-globulin, prothrombin activity as measured by the prothrombin time might be relatively low, if factor VII activity were low. If prothrombin time is the expression of the rate of thrombin formation, factor VII variations in different species seem to be more correlated with this rate than do variations of Ac-globulin. Such data suggest, therefore, an accelerating mechanism for factor VII under such circumstances. Variations of Ac-globulin do not seem to influence the rate of thrombin formation as much as factor VII does.

Another conclusion can be drawn from these experiments. Prothrombin time should be considered as a composite effect of at least three factors, prothrombin, labile factor or Ac-globulin, and factor VII. Essentially, however, it reflects, under certain experimental conditions, variations in factor VII.

TABLE 2.—*Factor VII Variations in Defect and in Excess*

	Variations in defect	Variations in excess
Congenital	Hemorrhagic disease due to deficiency of factor VII or allied factors	
Acquired	1. Dicumarol; tromexan; compound 63 2. Liver diseases 3. Newborn	1. Late normal pregnancy (9th month) 2. Thromboembolic diseases

PHYSIOPATHOLOGIC VARIATIONS

Researches on factor VII and allied factors made it possible to better characterize the coagulation defect in several physiopathologic conditions. A provisional classification of factor VII variations is given in table 2.

A few cases of congenital, isolated defect of factor VII or allied factors are reported in the literature. They were actually analyzed in terms of the technics for SPCA[27] or proconvertin.[33] In these cases the bleeding tendency is associated with a marked decrease of the concerned factor, a prolonged prothrombin time, and a normal prothrombin consumption or utilization.[45]*

Among the acquired variations, the observations concerning the decrease of factor VII during anticoagulant therapy with dicumarine derivatives, have been extensively studied.[8, 37] There is agreement that factor VII, SPCA, co-thromboplastin, the stable factors of MacMillan and of Owen and Bollman, and proconvertin are all decreased under these conditions. According to some investigators, the variations of factors VII are earlier and more pronounced than those of prothrombin.[38] It has been suggested, therefore, that factor VII or factor VII + prothrombin determinations are actually more suitable than other tests for the control of anticoagulant therapy.[37, 38] Recent research has emphasized that factor VII preparations obtained from dogs treated with dicumarine derivatives show less pronounced factor VII activity than these obtained from normal dogs.[36] These results are in keeping with the different prothrombin yield obtained in the same experimental conditions.[39]

* Since this paper was submitted for publication, another case of congenital, isolated defect of factor VII has been described by Beaumont and Bernard.[48]

The factor VII deficiency observed in liver diseases and in the newborn is a finding to be added to our previous information of prothrombin and Ac-globulin or labile factor deficiencies[38, 40, 41] (fig. 2). Also by using the technics suggested for SPCA, similar results are obtained.[42]

Among the variations in excess of normal, the increase of factor VII in late normal pregnancy and in thromboembolic diseases should be considered as a sign of increased blood coagulability in such conditions.[36, 38, 40, 41, 46] Since other tests do not always detect this hypercoagulability, it might be suggested that factor VII determinations be applied to its clinical diagnosis.

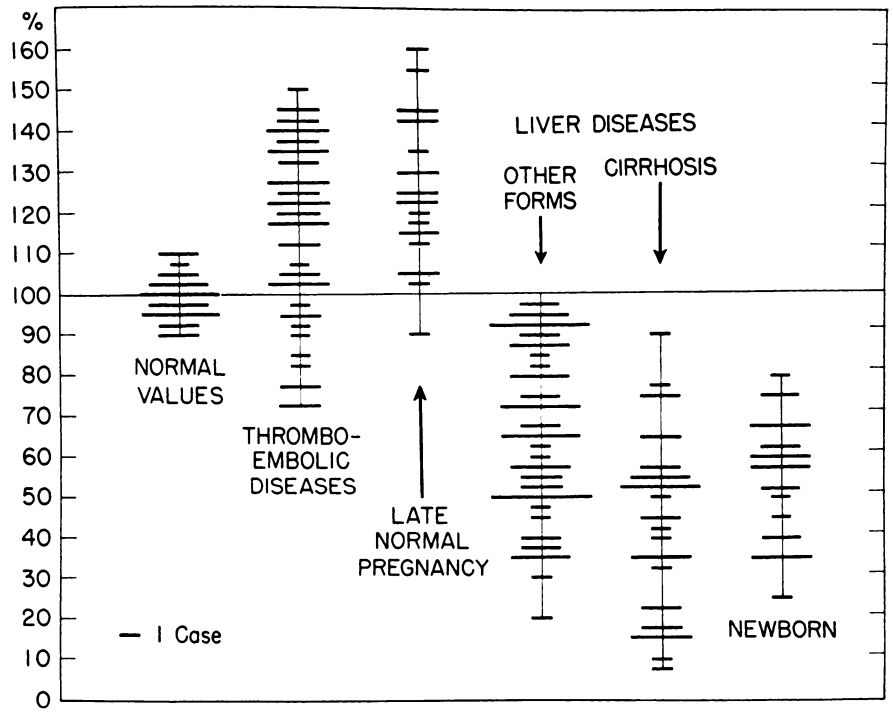

FIG. 2.—Factor VII values in various physiopathologic conditions: decreased factor VII activity in liver diseases and in the newborn; increased factor VII activity in thromboembolic diseases and in late normal pregnancy (9th month).

The variations of SPCA and of its precursor in conditions such as hemophilia and thrombocytopenia are believed to be secondary to variations of other factors and will, therefore, not be considered in this connection.

CONCLUSIONS

Although many data have been accumulated on the physiopathologic significance of factor VII, it is still questionable as to what extent it may be differentiated from prothrombin. The similar behaviour of factor VII and of prothrombin in a number of conditions suggests close relationships between the two factors in spite of the possible detection of isolated and nonassociated defects. Furthermore, from the physicochemical point of view, the properties of the two factors seem to be similar, and it is difficult to distinguish between them. The interpretation of SPCA and PCF effects on the basis of their being

precursors of prothrombin and not accelerators,[22] still deserves consideration. There is, however, some evidence that factor VII and allied factors are significant accelerators in the blood clotting mechanism. Further research on prothrombin derivatives[47] and on the development of an accelerator in stored purified prothrombin,[43] when correlated with other findings of the physiology and pathology, may clarify these matters. Finally, the newly described inhibitor of blood coagulation,[44] which is also contained in the barium carbonate adsorbate, should be analyzed in connection with factor VII and allied factors, in order to establish their reciprocal interrelationships.

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