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From the University Hospital, Medical Department A, Oslo, Norway

New Factors Concerned in the Coagulation of Blood

By Paul A. Owren

According to the classical theory built up by *Schmidt*, *Hammarsten* and *Morawitz*, coagulation takes place in two stages, and is illustrated by this well-known formula:

1. Prothrombin + Calcium⁺⁺ + Thrombokinase \longrightarrow Thrombin
2. Thrombin + Fibrinogen \longrightarrow Fibrin.

Prothrombin, calcium and thrombokinase react jointly during the formation of active thrombin. Thrombin reacts with the fibrinogen, whereby this is converted into fibrin.

In the course of time the classical doctrine has been subjected to numerous and abortive attacks. I will only mention that the colloid-chemical conception of blood coagulation has not survived the subsequent experimental tests, neither have the remaining non-thrombin theories been able to stand up to criticism.

With regard to the first stage of coagulation, the formation of thrombin, the majority of investigators agree with the formulation of *Morawitz* as far as the reacting substances are concerned, but opinions differ over the nature and conditions of reaction. The most important theories which differ from the classical doctrine with regard to this point, are those of *Bordet's* and *Howell*.

Bordet assumed that the prothrombin, which he terms serozyme, occurs in the circulating blood in an inactive form, possibly due to combination with an inhibitory substance.

Howell's theory requires that normally there is present a substance inhibiting coagulation by the formation of a prothrombin-antiprothrombin complex.

In spite of these theories, the just mentioned simple classical formulation of *Morawitz* has been generally accepted, and apart from the possible role played by heparin, no substances other than these four components have been recognized, which take part in the normal coagulation.

In the following a short report will be given on investigations which indicate that these generally accepted conceptions are incomplete. My

interest in the clotting problem was aroused by a case of hæmorrhagic diathesis, a 29 year old female, who was admitted into the University Hospital of Oslo in 1943. From the age of 3 years she suffered from severe and repeated nosebleedings, and constantly developed bluish subcutaneous marks and larger blood extravasations followed small traumas. Menstruation commenced at the age of 14 and was profuse and of long duration.

In the hospital in 1943 the ordinary organic examinations showed normal findings. Blood analysis showed normal values for Hgb. red cells, white cells and platelets. The bleeding time was normal, but the clotting time was greatly prolonged. Whole blood clotted in 25 mins. against normal time 6–10 mins. Prothrombin time by the method of *Quick* was 70 secs. against normal time 15–20 secs. Fibrinogen, calcium and ascorbic acid were found in normal concentrations.

It would seem natural to conclude that the hæmorrhagic diathesis was due to a prothrombin deficiency, as the prothrombin time recorded by *Quick's* method should correspond to a prothrombin concentration below 10 per cent of the normal, a value which according to experience is accompanied by a tendency to bleeding.

Hypoprothrombinemia to such a high degree is known only in conditions of K-avitaminoses and in severe hepatic damage.

A thorough clinical examination comprising hepatic functional tests revealed no indications for any lesion of this kind, and the condition was refractory to ingestion of large doses of vitamin K.

In view of these findings it was natural to doubt the correctness of *Quick's* method for prothrombin determination. In order to check the reliability of this method, small amounts of plasma from normal individuals were added to the plasma of the patient, and the prothrombin concentration was determined by *Quick's* method in the various mixtures. From the results it appeared that the prothrombin concentration apparently increased more quickly than was anticipated from the amount of plasma added.

Prothrombin was then removed from various samples of normal plasma by two adsorptions with $\text{Al}(\text{OH})_3$ followed by *Zeitz* filtration and variable quantities of this entirely prothrombin-free plasma were added to that of the patient.

The results are given in fig. 1 which shows that addition of prothrombin-free plasma caused diminution of the "prothrombin-time" of the patient, and consequently an apparent increase in the prothrombin concentration determined by the method of *Quick*.

Estimation of prothrombin by *Quick's* method failed, therefore, since

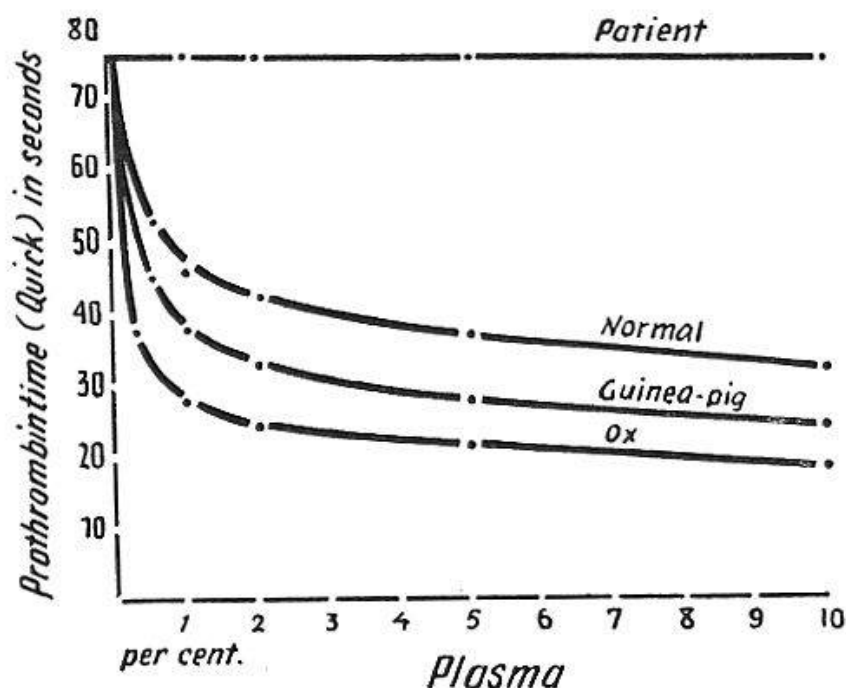


Fig. 1. The coagulation-stimulating effect on the patient's plasma of small amounts of prothrombin-free plasmas examined by the method of *Quick* for prothrombin determination.

the coagulation time varied independently of the prothrombin concentration and depended upon one or more additional factors in the prothrombin-free plasmas. This effect of prothrombin-free normal plasma was unchanged after removal of fibrinogen, and after *Chamberland* filtration.

Tests with different thrombokinase preparations proved that none of the preparations were capable of restoring normal conditions of coagulation in the patient's plasma. Fig. 2 illustrates this finding. The apparently reduced thrombokinase effect is uniform for all preparations.

Fig. 2. The correlation between maximal thrombokinase activity for different tissue extracts.

Thrombokinase	Coagulation time	
	Normal plasma	Patient plasma
Rabbit brain	14	58
Human brain	21	78
Placenta	12	53
Lung	16	68
Platelet emulsion: Normal	78	222
Platelet emulsion: Patient.	72	190
Physiological saline solution	120	365

The active factor which restored normal conditions of coagulation in the patient's plasma, therefore, could not be thrombokinase, prothrombin, calcium or fibrinogen.

On the basis of this and other confirmatory tests, it was justified to draw the following conclusions:

The blood of the patient lacks a substance found in normal blood, which is necessary for normal coagulation. This factor is not included in the classical coagulation doctrine or in subsequently introduced theories as to the course of the coagulation process. This factor I have termed the fifth clotting factor, abbreviated to factor V.

Factor V may be obtained from prothrombin-free plasma by fractional precipitation with ammonium sulphate (30–50 per cent saturation) followed by isoelectric precipitation (pH 5, 2–5,6).

This preparation has proved free from fibrinogen, prothrombin and thrombokinase. Addition of factor V to the patient's oxalated plasma produced a normal clotting time after recalcification both with, as well as without, addition of thrombokinase, as shown in fig. 3a and b.

Addition of factor V c. c.	Coagulation time in secs.
0.00	350
0.0125	170
0.025	140
0.05	115
0.10	90
0.20	85

Fig. 3a. Decrease in coagulation time for recalcified oxalated plasma on addition of factor V. (Patient with factor V deficiency.)

Fig. 3b. Coagulation time for plasma lacking factor V with optimal thrombokinase concentration and varying quantities of factor V. (Patient with factor V deficiency.)

Oxalated plasma c. c.	Thrombo- kinase c. c.	Factor V in buffer c. c.	Veronal buffer c. c.	CaCl ₂ (25 mM) c. c.	Coagulation time secs.
0.20	0.20	—	0.20	0.20	67.5
0.20	0.20	0.0025	0.1975	0.20	38.0
0.20	0.20	0.005	0.195	0.20	31.8
0.20	0.20	0.01	0.19	0.20	27.5
0.20	0.20	0.02	0.18	0.20	24.0
0.20	0.20	0.05	0.15	0.20	20.6
0.20	0.20	0.10	0.10	0.20	18.1
0.20	0.20	0.20	—	0.20	15.5

The intravenous injection of sterile factor V prepared from 200 ml. normal human plasma caused a shortening of *Quick's* prothrombin time from 65 to 28 secs., and a reduction of the clotting time with optimal recalcification of oxalated plasma from 340 to 170 secs. The effect of the injection disappeared in 3 days.

Experiments demonstrated that factor V was without influence on the thrombin-fibrinogen reaction. Its reaction is correlated with the first stage of the coagulation process, the thrombin formation.

In fig. 4 curve A_1 demonstrates the thrombin formation in a sample of defibrinated plasma from the patient on addition of thrombokinase and calcium. The thrombin is formed slowly. By addition of factor V, the velocity of the reaction increases rapidly as shown from curve A_2 . (The significance of the other curves is related to factor VI. See later.)

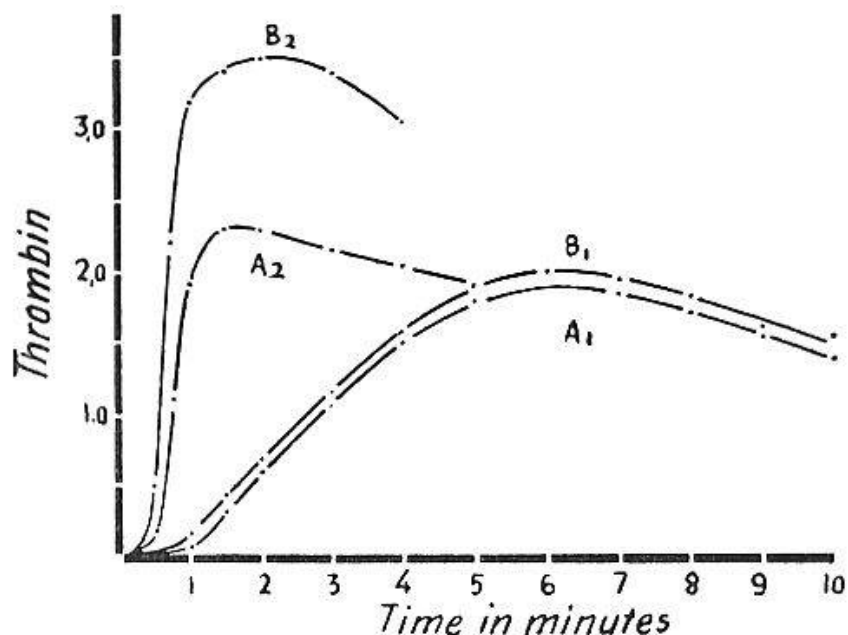


Fig. 4. Thrombin formation in defibrinated plasma with low and with high content of factor V, estimated with prothrombin-free oxalated plasma (A_1 and A_2) and oxalated plasma containing prothrombin (B_1 and B_2) respectively, as coagulation substrate. Curve A_1 and B_1 : Without addition of factor V. Curve A_2 and B_2 : With addition of factor V. Plasma from patient with factor V-deficiency. The ordinate gives thrombin formation in T. U. per 0.20 c. c. of a 15 per cent dilution of plasma.

The clotting anomaly in this case is caused, therefore, by a delayed conversion of prothrombin to thrombin in the presence of thrombokinase and calcium, owing to lack of factor V.

The examination of five hemophiliacs has shown that the concentration of factor V in hemophilia is normal. Factor V, therefore is not the globulin factor lacking in hemophilia, which factor has the same effect as thrombokinase. Thrombin formation in hemophilia is slow because of the delay in the liberation of active thrombokinase.

The new hemorrhagic disease, factor V-deficiency, I have termed "parahemophilia".

I will describe some experiments concerning thrombin formation with the use of isolated clotting factors. The methods for isolation are described in another paper (Owren, 1947).

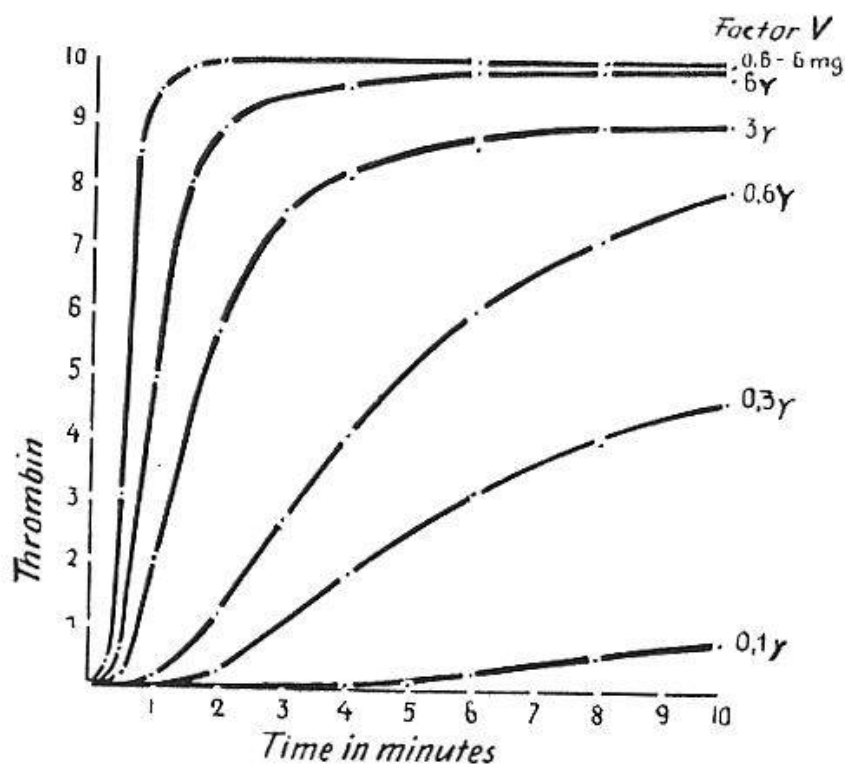


Fig. 5. Velocity of thrombin formation at optimal concentration of thrombokinase and calcium and varying amounts of factor V. Prothrombin: 10 P. U. per c. c. of the mixture. Thrombokinase: 0.2 g. acetone-treated human brain extracted with 5 c. c. physiological saline solution, of which 0.20 c. c. per c. c. of the mixture. Calcium: 2.5 mM. Temperature 37° C. pH. 7.3. Factor V is given in gamma of a dry preparation per c. c. of the mixture. The ordinate gives the thrombin formation in T. U. per c. c. of the mixture.

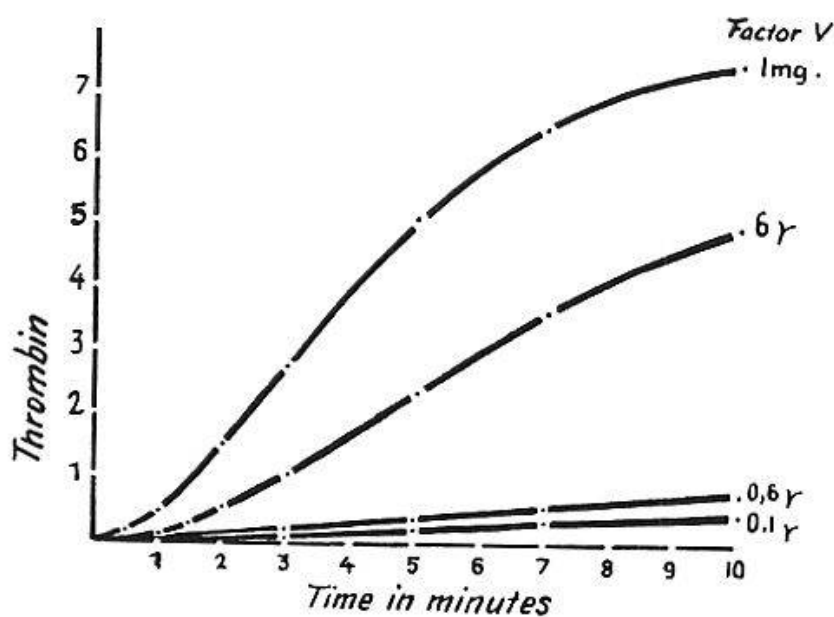


Fig. 6. Velocity of thrombin formation at low concentration of thrombokinase and varying amounts of factor V. Prothrombin: 10 P. U. per c. c. of the mixture. Thrombokinase: As in fig. 5, diluted to 1 per cent. Calcium: 2.5 mM. Temperature 37° C. pH. 7.3. The ordinate gives the thrombin amount in T. U. per c. c. of the mixture.

Fig. 5 demonstrates the thrombin formation in mixtures containing 10 P. U., optimal concentrations of thrombokinase and calcium, but with varying amounts of factor V.

The results demonstrate that the velocity of thrombin formation increases with increasing amount of factor V up to a certain limit. Increase of factor V above this limit is without further influence.

Fig. 6 shows the thrombin formation at *low* thrombokinase concentration with varying amounts of factor V. In general the effect of factor V is similar, but the maximal velocity with excess of factor V is considerably lower than with optimal thrombokinase concentration.

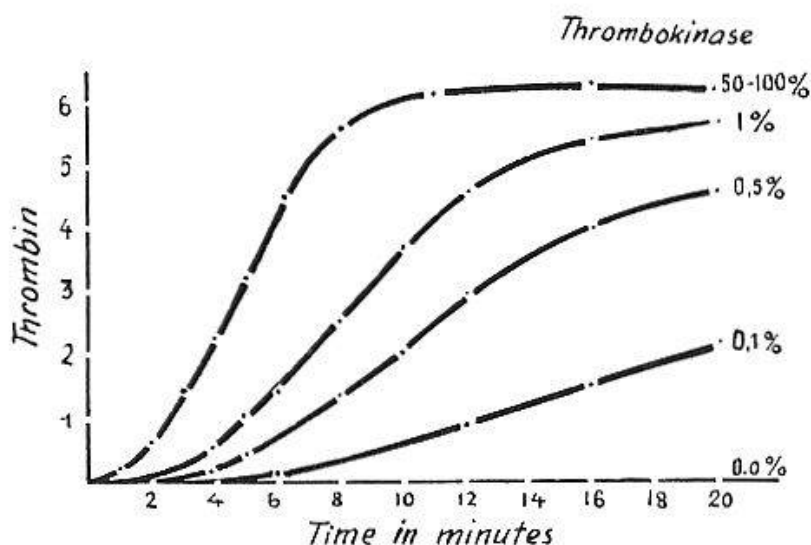


Fig. 7. Thrombin formation at *low* concentration of factor V, and varying thrombokinase concentrations. Prothrombin: 6.5 P. U. per c. c. of the mixture. Thrombokinase: (0.2 g. dried human brain extracted with 5 c. c. physiological saline solution – 100 per cent). Factor V: 5/10000 mg. of a dry preparation per c. c. of the mixture. Calcium: 2.5 mM. Temperature 37° C. pH. 7.3. The ordinate gives the thrombin amount in T. U. per c. c. of the mixture.

The influence of varying *thrombokinase* concentrations is illustrated by the following curves: Fig. 7 shows the thrombin formation at low concentrations of factor V with varying thrombokinase concentrations. The velocity of the reaction rises with increasing concentration of thrombokinase up to a certain limit in a manner corresponding to that demonstrated for factor V.

(Fig. 8 shows thrombin formation at high concentration of factor V and varying thrombokinase concentration. In general, the curves correspond to the last test.)

The experiments justify the following conclusion:

The rate of thrombin formation at constant prothrombin and calcium concentration increases with the concentrations of both factor V and

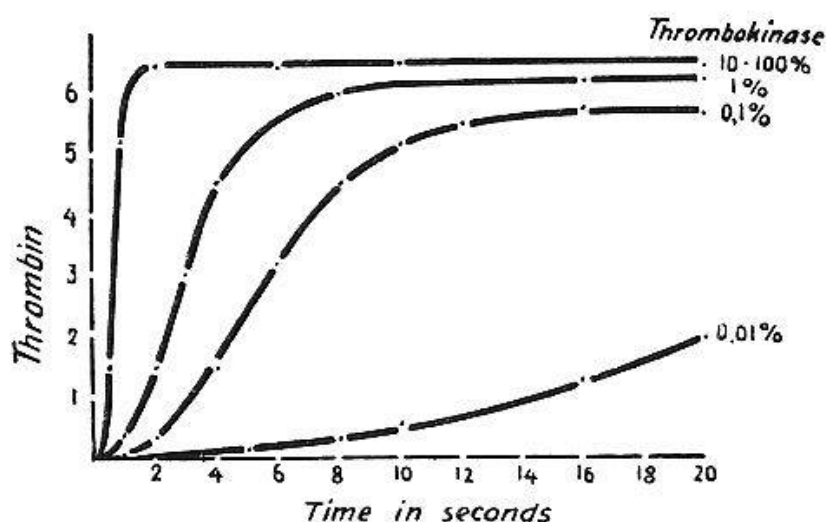


Fig. 8. Thrombin formation at *high* concentration of factor V and varying thrombokinase concentrations. Prothrombin: 6.5 P. U. per c. c. of the mixture. Factor V: Excess. Thrombokinase: Concentration as in fig. 3. Calcium: 2.5 mM. Temperature 37° C. pH. 7.3. The ordinate gives the thrombin amount in T. U. per c. c. of the mixture.

thrombokinase up to a certain limit. It is obvious from these experiments that the concentration of factor V will greatly influence the clotting time.

Fig. 9 demonstrates the clotting time in a mixture containing in addition fibrinogen with constant concentrations of prothrombin, thrombokinase, calcium and varying amounts of factor V. The clotting time decreases with increasing concentration of factor V to a limiting value and then keeps constant.

It follows from the investigations reported that thrombin formation

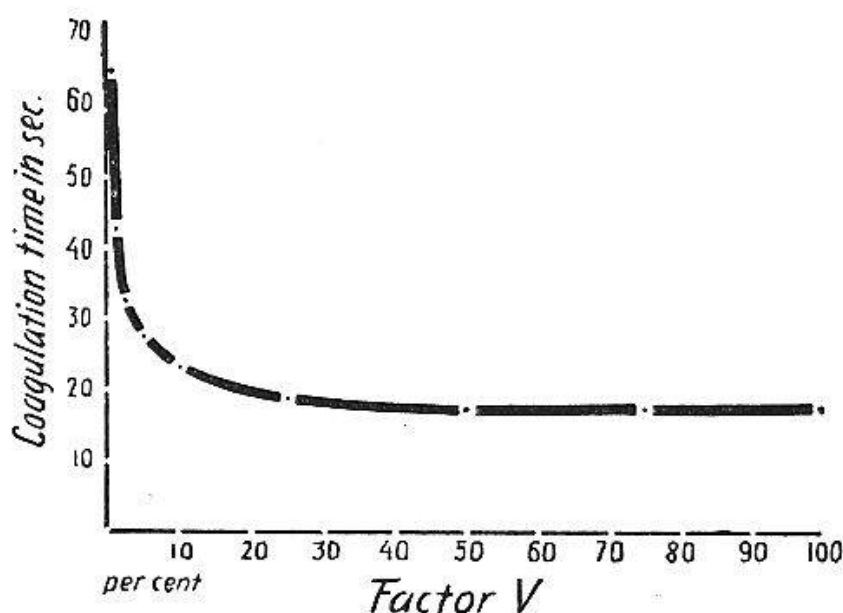


Fig. 9. Relation between coagulation time and concentration of factor V. Prothrombin: 20 P. U. per c. c. Thrombokinase: 100 per cent (concentration as in fig. 3). Fibrinogen: 0.10 per cent. Calcium: 2.5 mM. Temperature 37° C. pH. 7.3. The concentration of factor V has been given in per cent of an arbitrarily chosen solution.

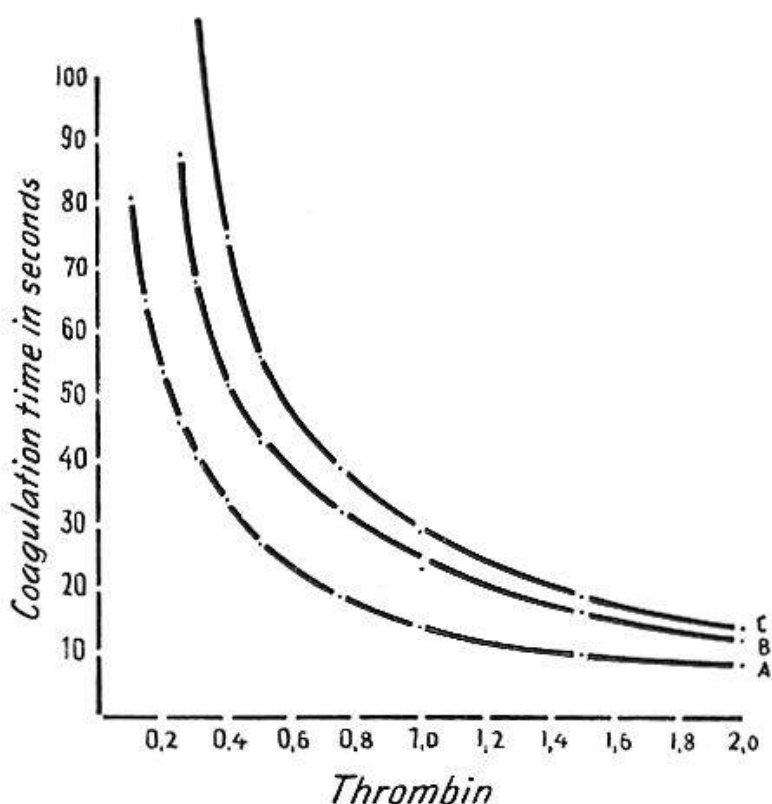


Fig. 10. The relation between thrombin concentration and coagulation time of the following coagulation substrates. A. Fibrinogen (0.10 per cent). B. Oxalated ox plasma diluted with an equal volume of buffer. C. Oxalated human plasma (undiluted). Coagulation mixture: 0.20 c. c. thrombin solution containing 2.5 mM calcium + 0.80 c. c. coagulation substrate. The abscissa gives thrombin amount (T. U.) in 0.20 c. c. of the thrombin solution.

may summarily be expressed by the following formula: Prothrombin + Factor V + Thrombokinase + Calcium \longrightarrow Thrombin.

In order to elucidate the actual mechanism of this process, I will describe certain peculiarities observed during estimations of the thrombin formed in the course of the reaction.

Thrombin is demonstrable only by its ability to coagulate fibrinogen and as clotting substrate for quantitative determination oxalated plasma as well as fibrinogen solutions may be used.

In fig. 10 curve A illustrates the relation between thrombin concentration and coagulation time of fibrinogen, curve B gives the corresponding relation for oxalated ox plasma diluted with an equal volume of buffer. (Curve C refers to undiluted human plasma.)

These curves are used for the determination of thrombin in solutions of unknown strength, from the clotting time of a definite amount of the solution with one or other of these substrates under standard conditions.

Solutions of pure thrombin give different clotting times for fibrinogen and oxalated plasma, but always the same concentration estimated with

use of these curves. Previous investigators have, to a great extent, used oxalated plasma also for determinations of the thrombin formed in a mixture of prothrombin, thrombokinase and calcium. They have taken for granted that the small amounts of calcium which are added to the oxalated plasma in the estimation of the thrombin formed, are removed rapidly by the formation of calcium oxalate, and consequently cause no activation of the prothrombin present in the oxalated plasma itself.

No investigations were made, however, to demonstrate the equivalence of fibrinogen and oxalated plasma in this respect.

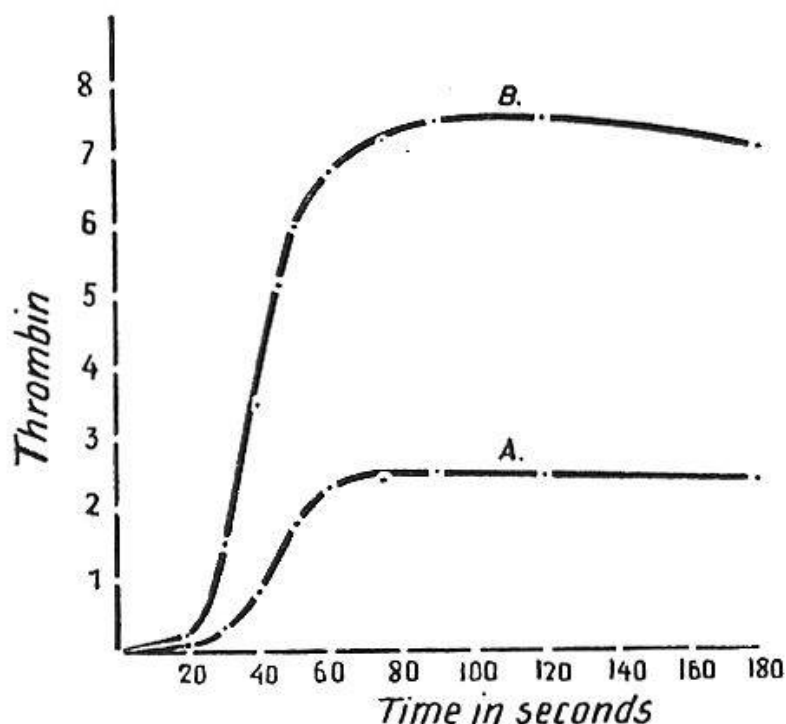


Fig. 11. Thrombin formation calculated per c. c. prothrombin conversion mixture registered with fibrinogen or prothrombin-free oxalated plasma (curve A) and with oxalated plasma containing prothrombin (curve B). Prothrombin: 2.5 P. U. per c. c. of the mixture. Thrombokinase: Optimal concentration. (Human brain). Factor V: Excess. Calcium: 2.5 mM. pH. 7.3. Temperature 37° C. Coagulation substrate: 0.40 c. c. plasma + 0.40 c. c. veronal buffer solution. The ordinate gives the thrombin amount in T. U. per. c. c. of the mixture.

Fig. 11 illustrates such an experiment. Curve A shows the thrombin formed in a mixture of prothrombin, factor V, thrombokinase and calcium, estimated with fibrinogen as coagulation substrate, and curve B gives the result, when oxalated plasma is used.

Rather surprisingly the oxalated plasma gives far higher values than fibrinogen. On the other hand, when prothrombin-free oxalated plasma is used, exactly the same values are found as with fibrinogen.

It is obvious, therefore, that the prothrombin conversion mixture must contain a substance capable of converting a certain amount of the

prothrombin of oxalated plasma into thrombin. Thrombin formation in the plasma itself is the only possible explanation of the difference between the curves A and B. It is further evident that the activating substance is not present in the mixture of prothrombin, thrombokinase, factor V and calcium at the beginning of the reaction shortly after their mixing. Initially there is no clotting of the plasma, and consequently no conversion of prothrombin to thrombin can have occurred in the plasma. The prothrombin activating substance, therefore, cannot be any of the four factors, prothrombin, thrombokinase, factor V or calcium.

The prothrombin activating substance appears just before or simultaneously with thrombin formation, but thrombin itself is unable to convert prothrombin to thrombin.

The substance, therefore, that activates the prothrombin in the plasma must be a previously unknown factor or principle which is formed during the process of converting prothrombin to thrombin. This principle is termed factor VI or preferably *prothrombinase* for reasons mentioned later, as it is not an original clotting factor in the same sense as the other five factors, but is formed during the process of coagulation.

By the simultaneous use of prothrombin-containing and prothrombin-free plasma as clotting substrate with standardised oxalate and prothrombin concentrations, it is possible to obtain information about the formation and activity of prothrombinase.

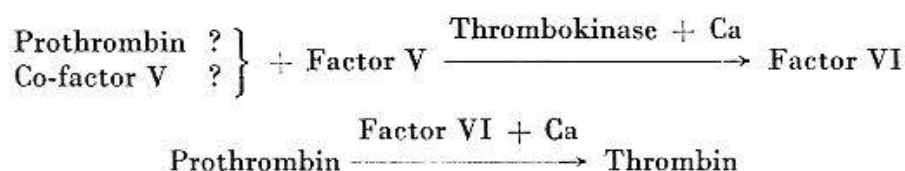
In this experiment (fig. 11) the difference between the curves is due to conversion of prothrombin in the prothrombin-containing plasma, and is a measure of prothrombinase activity.

Similar experiments revealed that the formation of prothrombinase is the necessary prerequisite for thrombin formation, and must be assumed to be the real principle which converts prothrombin to thrombin in the presence of calcium.

Factor V is of decisive influence on the maximal amount of prothrombinase which can be formed, and may probably be considered as a precursor of prothrombinase.

Thrombokinase seems to influence the velocity of the formation of prothrombinase but not the maximal amount formed.

In accordance with these results, the thrombin formation may be expressed by the following formula:



The first reaction needs the presence of a prothrombin preparation. Whether the factor needed is prothrombin itself or a necessary co-factor to factor V, which is present in the prothrombin preparation, is an unsolved problem.

The investigations reported form the foundation for the following conception of the mechanism of the coagulation process. When blood comes into contact with a foreign surface, thrombokinase is liberated and initiates the coagulation process. Thrombokinase acts by transforming or activating an inactive plasma substance, factor V, into an active substance, prothrombinase. This reaction needs the presence of calcium and prothrombin, or a factor that follows the prothrombin during the preparation. It could further be demonstrated that the formation of prothrombinase proceeds as an autocatalytic reaction. Once the reaction, therefore, is initiated, it should proceed without the presence of thrombokinase.

Prothrombinase is the real active substance, which, in the presence of calcium, converts prothrombin to thrombin. Thrombin then in the third stage, converts fibrinogen into fibrin. Besides antithrombin, the plasma also contains a substance able to inactivate prothrombinase.

There is evidence suggesting that in thrombin formation a splitting of prothrombin occurs, and prothrombinase could consequently be a type of proteolytic enzyme. This justifies the designation prothrombinase for this principle.

I have in this lecture only had an opportunity to demonstrate a few typical experiments, and not the whole basis for the conclusions drawn, but I hope the report given demonstrates the necessity for a new conception of the coagulation process in order to explain the experimental facts.

Experience from the history of coagulation research, has shown that new theories which conflict with the classical doctrine have a bad chance of surviving. It is satisfactory, therefore, to note that the new views by no means involve such a conflict, but only constitute new facts which naturally fall into the classical framework as a contribution to the development of the theory in the direction of greater completeness.

The new findings raise a great number of new questions and problems, but on the other hand they provide a rational explanation of many discordant experiments, conflicting results and unsolved problems in previous coagulation research.

The knowledge of factor V explains the variable convertibility of the prothrombin in different preparations, as well as in different clinical conditions. The assumption of variable convertibility was previously ne-

cessary to explain the great discrepancies between *Quick's* one stage and *Warner, Brinkhous, Smith's* two stage method for prothrombin determination, especially in studies on newborn infants and animals of various species. The problem as to which method is correct may be settled by saying that both methods have their defects which will be manifested in different ways under different circumstances.

The greatest unsolved problem in coagulation research of recent years, dates from 1935, when *Fisher* indisputably proved that an autocatalytic reaction takes place in this process, and *Astrup's* subsequent disproof of the old theory about the autocatalytic properties of thrombin. By transferring a small amount of clotting plasma to fresh plasma through a long series of chicken plasma samples free from thrombokinase, *Fisher* could demonstrate a coagulation activating substance which could be "cultivated" unlimitedly on steady inoculation in new plasma samples, multiplying just as a living organism. This mysterious vital growth of active substance has concealed a secret in the coagulation process. Any reasonable explanation of this peculiar phenomenon was not found. This substance seems to be prothrombinase.

From a clinical point of view, the new knowledge of the clotting process will demand investigations on factor V in different conditions and partly renewed investigations on prothrombin. The clotting problem from a clinical standpoint is not only concerned with delayed clotting and hemorrhagic diathesis, but to an even greater extent, with the question of increased coagulability and its relation to thrombosis and emboli. Future research on the coagulation process may enable those individuals who are threatened with thrombosis to be disclosed, and allow the adequate prophylactic measures to be taken.

Summary

An account is given of a woman with hæmorrhagic diathesis which had lasted since childhood. Prolonged coagulation-time and prolonged prothrombin-time by *Quick's* method were demonstrated. Investigations are submitted proving that the anomaly in coagulation was not due to deficiency of prothrombin or the other known clotting factors, but to the lack of a previously unknown coagulation factor named factor V.

The isolation of factor V and its function in the coagulation process are discussed. The formation of thrombin requires the presence of factor V, and the velocity of this reaction increases with increasing amounts of factor V up to a certain limit. Evidence is given for the assumption that this reaction falls into two stages: 1. the formation of the actual prothrombinconverting enzyme, termed prothrombinase, and 2. the conver-

sion of prothrombin to thrombin under the influence of prothrombinase in the presence of calcium. The formation of prothrombinase proceeds as an autocatalytic reaction.

The hæmorrhagic disease, factor V deficiency, is termed parahæmophilia.

Zusammenfassung

Es wird über eine Frau berichtet, die seit Kindheit an hämorrhagischer Diathese litt. Verlängerte Koagulationszeit und verlängerte Prothrombinzeit waren nachweisbar mit *Quicks* Methode. Es werden Forschungsergebnisse vorgelegt, die beweisen, daß die Koagulationsanomalie keine Folge eines Mangels an Prothrombin oder der anderen Gerinnungsfaktoren war, sondern des Mangels eines bis dahin unbekannten Koagulationsfaktors, der Faktor V genannt wird.

Die Isolation des Faktors V und seine Funktion im Gerinnungsprozeß werden diskutiert. Die Bildung von Thrombin erfordert die Gegenwart des Faktors V, und die Geschwindigkeit dieser Reaktion nimmt zu mit dem zunehmenden Vorhandensein des Faktors V hinauf bis zu einer bestimmten Grenze. Die Annahme wird begründet, daß diese Reaktion in 2 Phasen verläuft: 1. Die Bildung des gegenwärtigen prothrombinverwandelnden Enzyms, genannt Prothrombinase, und 2. die Verwandlung von Prothrombin zu Thrombin unter dem Einfluß der Prothrombinase bei Gegenwart von Calcium. Die Bildung der Prothrombinase geht als eine autokatalytische Reaktion vor sich.

Die hämorrhagische Krankheit, der Faktor-V-Mangel, wird Parahämophilie genannt.

Résumé

On rapporte l'observation d'une femme atteinte de diathèse hémorragique datant de l'enfance chez laquelle on a constaté un temps de coagulation et de prothrombine prolongé (méthode de *Quick*). Des recherches prouvent que l'anomalie de la coagulation n'était pas due à un manque de prothrombine ou d'un autre facteur de coagulation connu, mais au défaut d'un facteur de coagulation précédemment inconnu, nommé facteur V.

L'isolation du facteur V et sa fonction dans le processus de coagulation sont discutées. La formation de thrombine requiert la présence du facteur V, et la vitesse de cette réaction augmente en même temps que le facteur V jusqu'à une certaine limite. On apporte la preuve de l'hypothèse que cette réaction a lieu en 2 phases: 1° la formation de l'enzyme prothrombine, nommée prothrombinase, et 2° la conversion de la pro-

thrombine en thrombine sous l'influence de la prothrombinase en présence de calcium. La formation de la prothrombinase a lieu sous la forme d'une réaction autocatalytique.

La maladie hémorragique, par déficience en facteur V, est nommée parahémophilie.

Riassunto

Si describe l'osservazione di una donna colpita da diatesi emorragica sino dall'infanzia, nella quale si è constatato un tempo prolungato di coagulazione e di protrombina (metodo di *Quick*). Delle ricerche provano che l'anomalia di coagulazione proviene non da mancanza di protrombina o di un altro fattore di coagulazione conosciuto, ma dalla mancanza di un fattore di coagulazione precedentemente sconosciuto, chiamato fattore V.

Si discute sull'isolamento e sulla funzione del fattore V nel processo di coagulazione. La formazione di trombina esige la presenza del fattore V e la velocità di questa reazione cresce sino ad un certo limite coll'aumentare del fattore V. Si conferma l'ipotesi secondo la quale questa reazione si svolge in due fasi: 1.° formazione dell'enzima protrombina, detto protrombinasi e 2.° trasformazione della protrombina in trombina, sotto l'influenza delle protrombinasi in presenza di calcio. La formazione della protrombinasi è una reazione autocatalitica.

La malattia emorragica da insufficienza del fattore V si chiama paraemofilia.