Initiation of the Blood Coagulation Mechanisms

In the physiology of hemostasis the coagulation of the blood is one of the dominant events. When the complicated chemical interactions fail, persistent bleeding and even a fatal outcome may be expected. Since blood may remain fluid in the blood vessels for a lifetime, but nevertheless clot in a few minutes when shed, it is consequential to ask what initiates the complicated chemical interactions of the blood clotting mechanisms. Moreover, clotting of blood also occurs within the vessels themselves in association with the disease entities broadly referred to by the term thrombosis. As a health problem this perhaps ranks higher than the more spectacular bleeding episodes. It is now generally recognized that thrombosis is a major consideration in modern medicine, and has only a few other diseases as “competitors” in terms of the number of human beings afflicted. But statistics are not sufficient for evaluation of the ravages of thrombosis, for a select population is most frequently concerned; namely, the busy energetic contributors to those values associated with our progress. The afflicted one is apt to find thrombosis as a part of his living when he is of middle age, most productive and feeling the weight of responsibility.

The blood clot appears after a sol-gel transformation of plasma fibrinogen to fibrin. The enzyme thrombin is required for this. Since thrombin is derived exclusively from prothrombin our attention is directed to the conditions which favor the activation of prothrombin. With much labor and cost of time the prothrombin of the plasma has been obtained in purified form and thus it is possible to make observations concerning its activation not previously considered.

The simple view held for many years is that the transected cells adjoining the surface of a wound are rich in thromboplastin and that this activator mixes with blood as it flows over the surface of the wound. Prothrombin transforms to thrombin and thereafter fibrinogen clots. The usual notations are the following:

$$\begin{align*}
\text{Ca}^{++} & \\
\text{Prothrombin} & \text{Thromboplastin} & \text{Thrombin} \\
\text{Fibrinogen} & \text{Thrombin} & \text{Fibrin}
\end{align*}$$

This time honored viewpoint is essentially upheld by recently acquired chemical data, for when thromboplastin is prepared from tissues and mixed with calcium ions and purified prothrombin we do indeed obtain thrombin. It is incidentally interesting that only one other substance besides thromboplastin can function in that way. Admittedly one finds that the rate at which thrombin forms is slow, and much prothrombin becomes converted to a derivative of prothrombin that is not thrombin. The main fact, however, is that thrombin does appear. Once a small amount of thrombin has formed events unfold to give impetus to the effectiveness of thromboplastin and also to other reactions that can independently catalyze prothrombin activation. As soon as some thrombin forms a plasma protein, plasma Ac-globulin transforms to serum Ac-globulin, and thrombin is the only known substance associated with this activation. This may be noted as follows:

$$\begin{align*}
\text{Plasma Ac-globulin} & \text{Thrombin} \\
\text{Serum Ac-globulin}
\end{align*}$$

The small amount of thrombin also contributes to changes in platelets. Serum Ac-globulin greatly accelerates the interaction of thromboplastin, calcium ions and prothrombin, so that the thrombin concentration rises rapidly, even in the face of a certain amount of thrombin inactivation by antithrombin. Serum Ac-globulin occupies a much higher rank than it has heretofore been given in the literature. It is essential for several reactions that come into play. For example, without serum Ac-globulin platelet cofactor I does not function with platelet factor 3 to activate...
prothrombin. Without serum Ac-globulin, autoprothrombin also functions with platelet factor 3 in prothrombin activation. Thus, without serum Ac-globulin important functions of the platelets are in abeyance.

The platelets are auxiliary to thromboplastin in a manner only recognized recently. Like thromboplastin they alone with calcium may be mixed with purified prothrombin to obtain thrombin. In the presence of plasma Ac-globulin, calcium ions and material from platelets (platelet factor 3) a derivative of prothrombin forms in addition to some thrombin. This derivative is autoprothrombin and is a substance which does not itself become thrombin but greatly increases the effectiveness of thromboplastin.

In terms of the facts just reviewed, we can take the point of view that the initiation of the events in the chemical mechanisms of blood coagulation involves thromboplastin of tissue origin, and the most frequently occurring sequence of events is likely to be as follows:

\[
\begin{align*}
\text{Prothrombin} & \quad \text{Ca}^{++} \quad \text{Thromboplastin} \\
& \quad \text{Thrombin (slow reaction)} \\
\text{Plasma Ac-globulin} & \quad \text{Thrombin} \\
& \quad \text{Serum Ac-globulin} \\
\text{Platelets} & \quad \text{Foreign surfaces} \\
& \quad \text{Platelet materials} \\
\text{Ca}^{++} & \quad \text{Platelet factor 3} \\
& \quad \text{Ac-globulin} \\
\text{Prothrombin} & \quad \text{Thrombin} + \text{Autoprothrombin} \\
\text{Ca}^{++} & \quad \text{Serum Ac-globulin} \\
& \quad \text{Platelet cofactors} \\
& \quad \text{Platelet materials} \\
& \quad \text{Thromboplastin} \\
\text{Autoprothrombin} & \quad \text{Thrombin (rapid reaction)} \\
\text{Fibrinogen} & \quad \text{Thrombin} \quad \text{Fibrin} + \text{Cofibrin} \\
\text{Thrombin} + \text{Antithrombin} & \quad \text{Inactive thrombin} + \text{Some inactive antithrombin}
\end{align*}
\]

To regard the events outlined above as mechanisms whereby intravascular clots begin to form one postulates that thromboplastin gains access to the circulation. This could follow trauma, or the development of a lesion of a blood vessel wall. The amount of thromboplastin would need to be only a minute fraction of the enormous stores of thromboplastin known to be in the tissues. There is, however, another way in which intravascular clotting can be initiated.

It was mentioned earlier that thrombin is derived exclusively from prothrombin. The supporting evidence is that purified prothrombin may be dissolved in 25 per cent sodium citrate solution and it becomes thrombin by autocatalysis. This means that thromboplastin, as well as other materials of biological origin are dispensable in the activation of prothrombin. This implies the possibility of multiple prothrombin activation mechanisms, and makes it attractive to consider intravascular activation of prothrombin without thromboplastin. Without thromboplastin or other materials of cellular origin there remain only the platelets and all substances dissolved or otherwise dispersed in the plasma. If the blood specimen is drawn so that it comes in contact only with special surfaces that tend to maintain the integrity of platelets it can be centrifuged to remove all blood cells. The plasma then clots only very slowly if at all either in glass containers or in contact with water repellent surfaces. The slow clotting is indicative of slow prothrombin activation and upon analysis one finds most of it remaining in the specially collected platelet low plasma. Thus, without platelets or thromboplastin the activation of prothrombin may very well be insignificant. Platelets and plasma are, however, adequate for the activation of prothrombin and the clotting of plasma.

The major question is how can we account for the initial development of prothrombin activation? Once we can identify a pathway for obtaining a small amount of thrombin it is possible to derive serum Ac-globulin from plasma Ac-globulin. Then a whole series of reactions within the blood vessels themselves may follow and lead to prothrombin activa-
tion even though there be no thromboplastin or other materials from tissues. The platelets in combination with the platelet cofactors of plasma more than substitute for thromboplastin.

It is by means of platelets that we can account for the first small quantity of thrombin, and a plain experiment illustrates the fact. A mixture of purified prothrombin, calcium ions and platelet extract yields thrombin and simultaneously autoprosthenbin, the latter substance being an accelerator of prothrombin activation. Although thrombin is produced slowly at first by the interaction of platelets and prothrombin it is most likely sufficient to be followed by a series of events. Platelets are known to form aggregates and in that way could give rise to a high concentration of platelet materials in areas where the motion of the blood is slow. A sequence of events may then occur as follows:

\[
\begin{align*}
\text{Prothrombin} & \xrightarrow{\text{Ca}^{++} \text{ Platelet factor 3}} \text{Ac-globulin} \\
\text{Thrombin} & + \text{ Autoprothrombin (slow)} \\
\text{Plasma Ac-globulin} & \xrightarrow{\text{Thrombin}} \text{Serum Ac-globulin} \\
\text{Ca}^{++} & \text{ Serum Ac-globulin} \\
\text{Platelet factors} & \xrightarrow{\text{Prothrombin}} \text{Thrombin (rapidly)} \\
\end{align*}
\]

There is adequate laboratory information to support the view that these chemical events can occur as outlined, and presumably intravascular coagulation begins with those events where platelet materials are derived in some way in appreciable quantity from platelets. It is not intended to eliminate other possibilities from consideration. Since prothrombin may be activated in many different ways, it is only a question whether a substance can be at the appropriate place at a critical time. Intravascular prothrombin activation could possibly occur in association with other materials as, for example, lipids or trypsin and other enzymes. The unique information now available about thromboplastin and platelets is that they are exclusively the two factors that can be mixed with purified prothrombin to yield thrombin; and, this is most important for the activation of Ac-globulin which is a substance that is apparently indispensable for the coagulation of blood. Anatomically thromboplastin is in the fixed tissues and the platelets are in the plasma. For intravascular clotting to occur the thromboplastin must gain access to the circulation otherwise we can only describe mechanisms that begin with platelets. In the wound, both thromboplastin and platelets may function simultaneously to initiate events.

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Circ Res. 1956;4:126-128
doi: 10.1161/01.RES.4.2.126

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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