Fibrinolysis and "Fibrinolytic Purpura"

The study of the physiopathology of the hemostatic mechanisms has undergone revolutionary developments during the past twenty years. Extensive investigation has been devoted to the actions and abnormalities of the various coagulation factors, the naturally occurring anticoagulants, the functions and various deficiencies of platelets, and the function and anomalies of the vascular wall. An increasing amount of attention is now being given to the series of events which lead to the recanalization of the vessel after the hemostatic process has been completed. The enzyme fibrinolysin, by its ability to digest the fibrin clot, has a significant role in this phase. In the circulating blood, fibrinolysin is present as an inert proenzyme, which may on occasion become activated. The degree of this activation in normal and pathologic conditions depends on a delicate equilibrium between activators and inhibitors (diagram 1). This appears to be, at least partly, under the control of mechanisms of great importance in the general economy of the body. Thus, according to Ungar and Damgaard, the inactivation of fibrinolysin by antifibrinolysin may be regulated by ACTH and cortisone, and by at least two splenic factors of opposing activity. What role the equilibrium between fibrinolysin and antifibrinolysin might have on the level of circulating fibrinogen itself and on the size and texture of the fibrin clot remains to be clearly established.

Clinical observations often have the faculty of focusing attention on problems of a more basic nature. Thus, the importance of fibrinolysin in the pathogenesis of some hemorrhagic diatheses is becoming increasingly recognized and the interest in the subject of fibrinolysin revived. The activation of profibrinolysin to fibrinolysin is brought about by kinases which are found in many tissues. Tissue damage is, consequently, the best known factor causing activation of fibrinolysin. This has been detected in surgical trauma, burns and hemorrhage, shock, transfusion reactions, occasionally in severe parenchymal liver disease, in extensive pulmonary surgery and in disseminated carcinoma. Recently, a severe hemorrhagic disturbance in association with metastatic carcinoma of the prostate has been emphasized. Tagioni et al. have suggested that in these cases fibrinolysin may enter the circulation as such, being produced in excess by the widespread prostatic tissue. This concept finds support in the observation that a potent, active fibrinolytic agent, similar but not identical with plasma fibrinolysin, can be isolated from prostatic tissue. Finally, obstetricians have recently become familiar with the alarmingly severe hemorrhagic tendency which may accompany premature separation of placenta. The fundamental defect in this picture is pronounced hypofibrinogenemia or even afibrinogenemia. By some this is believed to be another example of activation of fibrinolysin due to the passage of placental tissue into the circulation. There is, however, no complete agreement on this interpretation and at least one author believes that the placental products entering the circulation are thromboplastic in nature and that afibrinogenemia is induced by extensive utilization of the protein due to intra-
vascular clotting. Since fibrinogen survives in the circulation for at least seventy-two hours, the sudden onset and severity of the hypofibrinogenemia suggest that this is probably not due to decreased production of the protein. In any event, patients who are saved are those in whom the uterus can be emptied promptly and who can simultaneously be given large amounts of fibrinogen.

In all these conditions, and particularly in those associated with carcinoma or extensive surgery, fibrinolysis may cause a complete breakdown of the hemostatic mechanism to an extent seldom observed in other hemorrhagic diatheses. The severe bleeding manifestations which follow ("fibrinolytic purpura") are probably due to enzymatic digestion not only of the fibrin clot but also, as indicated by survival studies of these agents in vivo, of fibrinogen and, in some cases, of all other proteins involved in the process of blood coagulation. Thus, fibrinolysis should be considered in the presence of a bleeding disease which cannot be explained by other more obvious causes. It should also be considered when many coagulation factors appear to be involved simultaneously. At least qualitatively fibrinolysis can be detected with simple laboratory methods.

Treatment of patients with severe "fibrinolytic purpura" has thus far been a difficult problem. Until the cause for activation or production of fibrinolysis has been removed, administration of whole blood, plasma and its fractions may be largely ineffective. The reason is that the coagulation proteins which are needed to restore the hemostatic process to normal are utilized and destroyed at a greatly accelerated rate. Moreover, removal of the cause often requires extensive surgical procedures which, in the presence of fibrinolysis, may prove very hazardous. A vicious circle is thus created and in some instances may be fatal. Newer therapeutic procedures, however, may soon be developed. Tagnon et al. have apparently isolated a specific inhibitor of prostatic fibrinolysin, effective in vivo as well as in vitro. There are indications that cortisone may also reduce the activity of fibrinolysin and stilbestrol may be specific, in certain cases of disseminated cancer of the prostate.

* Plasminogen, tryptogen, prolysins, lytic factor.
† Plasmin, tryptase, lysins (tissues).
‡ Fibrinolysokinase, fibrinokinase.
§ Antiplasmin
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cedures has often been responsible in the past for a renewed interest in a special field. It is likely that interest in the hemorrhagic conditions associated with high content of circulating fibrinolysins may result in a revival of interest in this remarkable agent and its relationship to the physiopathology of hemostasis.

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