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Alkjaersig N, Fletcher A P & Sherry S. The mechanism of clot dissolution by plasmin. *J. Clin. Invest.* 38:1086-95, 1959.
[Dept. Med., Washington Univ. Sch. Med., St. Louis, MO]

In this paper we described *in vitro* experiments and *in vivo* observations concerned with thrombolytic mechanisms. Since plasminogen is found in plasma and also is a constituent of thrombi, clot lysis occurs by a dual mechanism. The primary mechanism of thrombolysis involves the diffusion or adsorption of plasminogen activator to the thrombus, activation of intrinsic clot plasminogen, and thrombolysis. The secondary mechanism involving digestion of the thrombus by extrinsic plasmin action appears to be of negligible importance. [The *SCI*® indicates that this paper has been cited in over 550 publications since 1959.]

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"This paper, published simultaneously with two clinical investigative studies,[1,2] appeared at a time of considerable controversy in the developing field of thrombolytic therapy. Essentially, it had been shown that clot lysis (thrombolysis) could be produced in the experimental animal by infusion of several proteolytic enzymes including 'plasmin' preparations (subsequently shown to contain high concentrations of streptokinase), or by streptokinase (a plasminogen activator) alone. Fortunately, one of my colleagues had been invited on an extensive tour of US nuclear facilities during the preparatory phase of the 1955 Geneva conference on 'Atoms for Peace' and had returned convinced of the potential inherent in radiochemical assay methods. The developing of an assay for thrombolytic activity based on the use of ^{131}I labeled fibrin greatly facilitated studies showing the major importance of plasminogen activator and the relatively minor effect of enzymes such as plasmin on clot lysis.

"At that time, it was difficult to see how an *in vivo* fibrinolytic state could be achieved, since it was already known that plasma contained greater inhibitory capacity than the potentially available plasmin. *In vitro* experiment, however, showed that much greater fibrinolysis than fibrinogenolysis occurred when a plasminogen activator was introduced into a plasma-clot system; consequently a mechanism existed which favored lysis of thrombi and at the same time protected the blood coagulation system. Further experiments indicated that plasminogen was adsorbed onto the clot, where, when activated, it was in close proximity to its substrate, fibrin, and in a relatively inhibitor-free environment. Initially, it was difficult to accept that plasminogen was adsorbed to the clot, since there was little difference in plasminogen content of plasma and serum; however, washed clots could be ground up and extracted and did indeed release measurable plasminogen. Later, it was shown that approximately four percent of the plasminogen is bound to fibrin.[3]

"These *in vitro* studies, together with earlier studies on the clearance rate of streptokinase, formed the basis for determining doses and infusion rate, and for defining the necessary laboratory measurements to ensure an active fibrinolytic state and an adequate blood coagulation system.

"Our original concern over introducing a hemorrhagic diathesis by the infusion of streptokinase has been obviated by newer plasminogen activators, first urokinase, which has a more favorable ratio of fibrinolysis to fibrinogenolysis than streptokinase, and most recently by the development of tissue plasminogen activator, which is capable of lysing clots *in vivo* with little, if any, effect on the coagulation system. Collen and others have been especially active in this area, and a review by Collen[3] outlines the development of this activator, and summarizes the more recent developments in the biochemistry of fibrinolysis.

"When I joined Sol Sherry, he was chief of the Medical Service at the Jewish Hospital of St. Louis, where Tony Fletcher soon joined as well. The early part of these studies took place there, but, shortly after, we moved to Barnes Hospital; throughout, all three of us held appointments at Washington University. My clinical investigator colleagues were excited by the avenues opened by the plasminogen activators as thrombolytic agents and were instrumental in designing the *in vitro* experiments. We were all overjoyed to find the *in vivo* studies correlating so well with projections.

"I think that this paper has been referred to frequently because, with the accompanying clinical studies, it offered a rational basis for the use of plasminogen activators as thrombolytic agents and also because of interest in the methodology employed."

1. **Fletcher A P, Alkjaersig N & Sherry S.** The maintenance of a sustained thrombolytic state in man. I. Induction and effect. *J. Clin. Invest.* 38:1096-110, 1959. (Cited 225 times since 1959.)
2. **Fletcher A P, Sherry S, Alkjaersig N, Smyrniotis F E & Jick S.** The maintenance of a sustained thrombolytic state in man. II. Clinical observations on patients with myocardial infarction and other thromboembolic disorders. *J. Clin. Invest.* 38:1111-19, 1959. (Cited 100 times since 1959.)
3. **Collen D.** On the regulation and control of fibrinolysis. Edward Kowalski Memorial Lecture. *Thromb. Haemost.* 43:77-89, 1980.

