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SOME OBSERVATIONS ON THROMBOLYSIS *in vitro*<sup>1</sup>

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 (Department of Haematology, Radcliffe Infirmary, Oxford) The widely accepted intrinsic clot lysis theory (Alkjaersig, Fletcher, and Sherry, 1959) as a primary mechanism of thrombolysis postulates that during formation of thrombi plasma plasminogen adsorbed on to the fibrin/clot surface is activated by circulating plasminogen activators with resultant autodigestion of the thrombus.

Studies in this laboratory have revealed that the plasminogen content of plasma, before and after the formation of artificial thrombi by Poole's modification of the Chandler tube method (Poole, 1959), was not altered, more than 90% of the original plasminogen content of the plasma being recoverable in the defibrinated plasma. Furthermore, the plasminogen content of washed and drained artificial thrombi was uniformly low, and any exogenously added plasminogen was easily washed out of the thrombus.

Similarly, the plasminogen content of human thrombi formed spontaneously over plastic surfaces in contact with a circulation *in vivo*, and that of fresh and unorganized native (*in vivo*) thrombi obtained by operative intervention, without exception, was low.

In an artificial circulation, lysis of Chandler tube thrombi prepared from native blood, or plasma, or from recalcified platelet-rich or platelet-depleted citrated human plasma could not be readily achieved by perfusion with a wide variety of concentrations of plasminogen activators in saline-buffer or plasma. On the other hand, perfusion with human plasmin (grade A, Kabi) in saline led to predictable thrombolysis, the rate of lysis being the function of the enzyme concentration used.

From this study, it has been possible to place recent and unorganized native (*in vivo*) thrombi and emboli into three broad categories: (1) thrombi and emboli, which were deficient in intrinsic plasminogen; (2) thrombi and emboli which, apart from containing only trace amounts of plasminogen, were also rich in an antiplasmin-like activity; and (3) thrombi and emboli which were deficient in plasminogen but rich in a plasminogen activator.

In an artificial circulation, thrombi of the first category behaved similarly to the Chandler tube thrombi, definite lysis only occurring when perfused by human plasmin. Thrombi in the second category failed to lyse with both plasminogen activators and with low concentrations of plasmin; however, when treated by agents known to induce a 'peptone effect' (Astrup, 1968), successful thrombolysis could be achieved with low concentrations of plasmin. Thrombi in the final category lysed slowly but spontaneously, and it was possible to enhance the rate of lysis by perfusion with plasminogen activators.

The physico-chemical properties of the plasminogen activator isolated from saline extracts of thrombi of the latter category were different from those of tissue activators of plasminogen, leukoproteases, urokinase, and streptokinase (Dalal, Shah, Allington, and Sharp, 1969).

Recent unorganized thrombi and emboli of all categories were found to be permeable to various blood components, including plasma plasminogen and antiplasmins, and it was possible to flush red cells out of such thrombi by prolonged gentle perfusion finally leaving a pearly white coralline network of fibrin.

On the basis of these and our other findings, it is suggested that the selective thrombus activator of plasminogen binds with a globulin fraction of plasma and that this complex activates the plasminogen permeating through the thrombus mass to an enzymatically active plasmin-globulin complex. This complex could not be inhibited by circulating antiplasmins. Thus this enzymatically active plasmin-globulin complex could digest the fibrin core of a thrombus in the presence of circulating antiplasmins and it is suggested that this may be the mechanism responsible for thrombolysis *in vivo* (Dalal, P. M., Shah, P. M., Sharp, A. A., and Allington, M. J., 1969).

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<sup>1</sup>This work was supported by a grant from the Wellcome Foundation.

## THROMBUS DISSOLUTION

A. A. SHARP (Department of Haematology, Radcliffe Infirmary, Oxford) Thrombi have been assumed by many to be standard units made up of fibrin interspersed with platelets, red cells, and white cells and we tend to assume that all thrombi are equal in the eyes of God. Yet it must be obvious to all that there are thrombi and thrombi and that the nature of the fibrin matrix must vary depending on the site of thrombus formation.

Studies in our laboratory have shown that there are considerable differences between fibrin clots formed in a test tube, those formed artificially in a Chandler tube *in vitro*, and those native thrombi formed *in vivo*. Further, there are considerable differences between a thrombus formed on the wall of a vessel, and a thrombus occluding an artery or vein. There are also differences between fresh and old thrombi, age having a variable influence on morphology. When considering thrombolysis there appear to be thrombi which can lyse spontaneously, those which can be lysed by extraneous factors, and those which can never lyse or be lysed (Dalal, Shah, Sharp, and Allington, 1969). Also when certain thrombi are perfused, the perfusate can be shown to pass easily through the interstices of the fibrin, washing out the red cells and trapped plasma. Therefore, it is reasonable to assume that even occluding thrombi may allow the