LOCAL FACTORS IN THROMBOLYSIS

A. S. TODD (Department of Pathology, The University of Dundee) It has been shown that the activator of plasminogen in tissue is concentrated in the endothelium of blood vessels, especially that of veins and venules (Todd, 1959). Recently, by modifying the time and temperature of incubation (4°C for 24 to 48 hours), the histological technique for identifying plasminogen activator ('fibrinolysis autography') has been improved enabling a greater range of activator concentrations to be detected within a single preparation. This modification has now been used in the study of thrombosis. It is found that the endothelium adjacent to thrombus in veins, pulmonary arteries, cardiac atria, and coronary arteries contains activator. In cases where the thrombus has been loosened, activator can be detected on the fibrin surface, and sometimes lines and foci of activator are found buried within the thrombus, apparently trapped after retraction and rethrombosis. A similar distribution of activator can be demonstrated in pulmonary emboli. Most of the coronary thrombi examined were rich in plasminogen activator. It is, therefore, reasonable to assume that plasminogen activator from endothelium in the venous and coronary circulation plays a major part in the loosening of thrombus and the detachment of emboli.

The endothelium of thrombosed systemic arteries rarely shows fibrinolytic activity, although foci of activator are found deep within mural thrombi from heart chambers and great vessels, apparently related to leucocytes. The platelet-rich line of Zahn appear to be resistant to plasmin digestion, thus accounting for their prominence in older thrombi.

Coronary and intramyocardial arteries normally show activator in the endothelium, although at lower concentrations than that in veins of comparable size. The degree of fibrinolytic activity seems unrelated to the amount of intimal thickening. Renal arterioles and glomeruli are also active to about the same extent.

Experiments with vessels from limbs subjected to ischaemia during amputation show that the arteries can develop activator concentrations equivalent to those found in veins. Thus, fibrinolytic activity in arteries may be controlled by stimuli of metabolic origin related to the efficiency of their blood supply.

REFERENCE


A further paper on fibrinolysis in animals was read by Dr Chushne Hawkey.

PHARMACOLOGICAL ENHANCEMENT OF FIBRINOLYSIS

G. R. FEARNLEY AND R. CHAKRABARTI (Gloucestershire Royal Hospital, Gloucester) The discovery that normal blood has spontaneous fibrinolytic activity (Fearnley and Tweed, 1953) due to a plasminogen activator (Flute, 1960) which is adsorbed to fibrin clot (Fearnley, 1953), led to a concept of 'fibrinolysis by adsorption' (Fearnley, 1953, 1961). The situation in veins may differ somewhat from that in arteries since blood fibrinolytic activity appears to derive mainly from the venous side of the circulatory system, and in veins fibrinolysis may be an important function of contiguous vascular endothelium. Evidence has been obtained of an association between defective blood fibrinolytic activity and coronary artery disease and that the former may adversely affect prognosis (Chakrabarti, Fearnley, Hocking, Delitheos, and Clarke, 1966; Chakrabarti, Hocking, Fearnley, Mann, Attwell, and Jackson, 1968).

Over the past 10 years a number of drugs given orally, including the sulphonylureas, the biguanides, and anabolic steroids, have been discovered to increase blood fibrinolytic activity but resistance, in this respect, eventually develops (Fearnley, 1964). Latterly phenformin or metformin combined with the anabolic steroid ethyloestrenol have been found to produce a pronounced and sustained increase in blood fibrinolytic activity, together with reduction of plasma fibrinogen levels in a majority of patients with occlusive vascular disease (Fearnley, Chakrabarti, and Hocking, 1967). In addition to these effects, phenformin plus ethyloestrenol decreases platelet stickiness and serum cholesterol levels, whereas metformin plus ethyloestrenol has an adverse influence on both these measurements (Chakrabarti and Fearnley, 1967; Fearnley, Chakrabarti, and Evans, 1968a). Clofibrate (Atromid-S) though effective in reducing serum cholesterol and plasma fibrinogen, has been found to have only a temporary effect on platelet stickiness; and, in contrast to the original Atromid which contained androsterone, to have antifibrinolytic properties, as judged by prolongation of the dilute blood clot lysis times of patients treated with this drug (Fearnley, Chakrabarti, and Evans, 1968b). Recent studies in our laboratory indicate that treatment of arteriopathic patients with phenformin plus ethyloestrenol is associated with a pronounced increase of fibrin degradation products, which provides the first evidence that an increase of blood fibrinolytic activity as measured in vitro is accompanied by the breakdown of fibrin/fibrinogen in vivo. Hence this combination of drugs appears to produce therapeutic defibrination. Phenformin plus ethyloestrenol, because of its favourable and sustained effects on four factors associated with ischaemic disease, i.e., fibrinolysis, plasma fibrinogen, platelet stickiness, and serum cholesterol, would seem to be suitable for trial as a prophylactic measure in survivors of vascular occlusions.

REFERENCES