

## ***This Week's Citation Classic***

**Todd A S.** The histological localisation of fibrinolysin activator. *J. Pathol. Bacteriol.* **78**:281-3, 1959. [Dept. Pathol., Royal Victoria Infirmary, Newcastle upon Tyne, England]

A histochemical method for the study of fibrinolytic activity in tissues was devised, using a thin fibrin film as a substrate. It was shown that in human tissues most of the plasminogen activator is concentrated in the endothelium of blood vessels, especially veins. [The **SCJ**<sup>®</sup> indicates that this paper has been cited over 440 times since 1961.]

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"From 1946-1949, J.B. Duguid published his observations on the incorporation of fibrin into the walls of coronary arteries, on which he based his revival of Rokitansky's thrombogenic theory of atherosclerosis.<sup>1</sup> By the time I came to work in Duguid's department at Newcastle the theory had created considerable interest among those working on blood coagulation, and he himself was writing that 'in considering the aetiology of atherosclerosis attention must be turned to the blood and the factors in blood which govern thrombosis.' I saw fibrinolysis as one such factor and with Duguid's encouragement began to study fibrinolytic activity in blood. During a time of setback in this work I realised that we knew little of the role of cells and tissues in the fibrinolytic process, and that as a morphologist I was better equipped for the study of these problems than for the more orthodox biochemical approach. It was well known that plasminogen (fibrinolysin) activator was abundant in tissues, associated with the microsomal fraction of cellular homogenates, but its distribution between cells of different types was unknown.

"My approach to the problem of the cellular

distribution of plasminogen activator was to scale down the classical 'fibrin plate technique' in which tissue fragments were incubated on a layer of fibrin formed in a petri dish. Instead the fibrin was deposited as a thin film on a microscope slide and the tissue was applied as a fresh frozen section.

"The first preparations were almost a failure since the sections floated off the substrate during fixation and staining so that direct correlation of areas of fibrin digestion with the structures in the section was impossible. However, the fibrinolytic activity was so intense, so focal, and distributed in such a striking pattern that it was possible to deduce that it had originated from blood vessels. The precise localisation was due to the lucky chance that the enzyme is very firmly bound to the tissues. In later preparations I was fortunate enough to see fibrinolytic activity related to cells peeling off a vein wall, thus getting a clue to the endothelial origin of the enzyme.

"It is hard to say why the paper should have been so much quoted. First, I must acknowledge the generosity of fellow writers. Secondly, the observations filled a gap between measurements of the enzyme in extracts of whole tissues or in subcellular fragments. Thirdly, the observations were visually satisfying and simple to interpret; one could see the tissues dissolving the fibrin, as they may do in life. Finally, the observations revived the view that endothelium plays an active part in the maintenance of blood fluidity, fulfilling John Hunter's prediction that '...where there is a full power of life the vessels are capable of keeping the blood in a fluid state,'<sup>2</sup> lending support to Copley's idea<sup>3</sup> of a dynamic balance between fibrin formation and dissolution at the plasma-tissue interface and providing a cellular explanation of the localised nature of the process of thrombosis. More recent work has been reported in 'Plasminogen activators—a morphologist's view.'<sup>4</sup>

1. **Duguid J B.** Pathogenesis of atherosclerosis. *Lancet* **2**:925-7, 1949.

2. **Hunter J.** *A treatise on the blood, inflammation and gunshot wounds.* London: E. Cox, 1812. p. 40.

3. **Copley A L.** Fibrinolysis and atherosclerosis. *Lancet* **1**:102-3, 1957.

**Todd A S.** Plasminogen activators—a morphologist's view. *J. Clin. Pathol.* **33**(Suppl. 14):18-23, 1980.