This Week's Citation Classic™ CC/NUMBER 41 OCTOBER 8, 1984

Astrup T & Müllertz S. The fibrin plate method for estimating fibrinolytic activity. *Arch. Biochem. Biophys.* 40:346-51, 1952.
[Biological Institute, Carlsberg Foundation, Copenhagen, Denmark]

This paper gives a description of the optimum conditions of the fibrin plate method, thereby making possible the accurate assessment of small quantities of fibrinolytic agents. [The *SCI*® indicates that this paper has been cited in over 1,060 publications since 1955.]

Tage Astrup
Section of Coagulation and Fibrinolysis
Department of Clinical Chemistry
Ribe County Hospital
and
Section of Thrombosis Research
South Jutland University Centre
6700 Esbjerg
Denmark

June 13, 1984

"The roots of this paper go back in time to the mid-1930s. The study of mammalian cells grown *in vitro* was in its adolescent stage with numerous unsolved problems. The chicken plasma clot providing the solid matrix for the growing cells was often seen to undergo a process of liquefaction causing the cell culture to collapse. This occurred most frequently when the cultivation of explants from certain epithelia and tumors was attempted. It was a major goal of the Copenhagen Institute (headed by Albert Fischer) to elucidate the particular interactions between the cells and their substrates causing this liquefaction.

"In those days, this was not an easy task. Methods for the production of sufficient quantities of purified fibrinogen and thrombin had to be worked out first. To emulate conditions in tissue culture, solutions of bovine fibrinogen were clotted in a petri dish with bovine thrombin forming a layer of fibrin, on the surface of which samples of tissue or drops of lytic solutions could be placed causing the formation of areas of lysis. Thus was born the fibrin plate method. The first major result of its application was the discovery of the tissue plasminogen activator.[1] Subsequently, the method was standardized, resulting in the publication cited here. Among important, early findings were the demonstration by Sten Müllertz[2] of a plasminogen activator in blood, and the observation by Olesen[3] that a plasminogen activator is generated from a humoral precursor by acid polysaccharides (now called the intrinsic system of fibrinolysis). The method made possible the quantitative assay of the small amounts of plasminogen activator usually present in human and animal tissues.[4] The method became popular because of its simplicity and sensitivity, and because it simulated conditions in the body, but many investigators encountered difficulties in mastering the technique. This was chiefly caused by the use of inferior grades of plasminogen-rich fibrinogen. Conditions have been worked out in detail,[5] the latest test of precision appearing recently.[6]

"Müllertz, now professor and head of the department of clinical chemistry at the Hvidovre Hospital and the University of Copenhagen, has retained his interest in fibrinolysis. I transferred my research activities to Washington, DC, in 1961, supported by a grant from the National Heart, Lung, and Blood Institute, National Institutes of Health. Having retired in 1976 to my native country, I am happily continuing research in blood coagulation, fibrinolysis, and thrombosis in my home town, Esbjerg, aided by dedicated and highly qualified colleagues and associates. For this I owe a debt of gratitude to good fortune."

1. **Astrup T & Permin P M.** Fibrinolysis in the animal organism. *Nature* 159:681-2, 1947. (Cited 175 times since 1955.)
2. **Müllertz S.** A plasminogen activator in spontaneously active blood. *Proc. Soc. Exp. Biol. Med.* 82:291-5, 1953.
3. **Olesen E S.** Peptone activation of a serum fibrinolytic system. *Acta Pharmacol. Toxicol.* 15:197-206, 1959.
4. **Astrup T & Albrechtsen O K.** Estimation of the plasminogen activator and the trypsin inhibitor in animal and human tissues. *Scand. J. Clin. Lab. Invest.* 9:233-43, 1957. (Cited 170 times since 1957.)
5. **Astrup T & Kok P.** Assay and preparation of tissue plasminogen activator. *Meth. Enzymology* 19:821-34, 1970.
6. **Jespersen J & Astrup T.** A study of the fibrin plate assay of fibrinolytic agents: optimal conditions, reproducibility and precision. *Haemostasis* 13:301-15, 1983.

