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Citation Classics

Ratnoff O D & Menzic C. A new method for the determination of fibrinogen in small samples of plasma. *Journal of Laboratory and Clinical Medicine* **37**:516-20, 1951.

The authors describe a simplified method for the determination of fibrinogen in plasma which permits the accurate and rapid determination of the amount of fibrinogen in samples of normal plasma as small as 0.1 ml, one tenth the amount used in methods previously described. [The *SCI*® indicates that this paper was cited 668 times in the period 1961-1975.]

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"The flattery implicit in having a paper among the top 500 is tempered by the realization that this is indeed a minor work, providing no new biological insights. When I returned to Johns Hopkins University School of Medicine after World War II, I began a series of studies of the fibrinolytic properties of plasma. Inevitably, I was drawn to an investigation of Jobling's[1] report that the crisis in pneumonia was associated with an increase in the proteolytic activity of serum. Analysis of the events that took place during the course of pneumonia required a rapid but accurate technique for measuring the concentration of fibrinogen in plasma, since this protein is a natural substrate of plasmin, a fibrinolytic enzyme that can be generated from its precursor, plasminogen. Earlier methods were either inaccurate, required large amounts of plasma, or were time-consuming.

"With the able collaboration of Mr. Calvin Menzie, who was Dr. C. Lockard Conley's technician, I devised a technique for capturing the fibrin that formed when diluted plasma was clotted by thrombin. We wound the fibers upon crushed glass, allowing us to separate the fibrin from other proteins with a minimum of effort We then determined the concentration of fibrin by the Folin-Ciocalteau technique, standardized against both a gravimetric and a chemical analysis for protein. Accurate results required only 0.5 ml of plasma, much less than other methods available at the time. I probably didn't explain this well in my text, for a prominent journal rejected the manuscript with the comment that the results I obtained with my micromethod were the same as with macromethods, and thus represented no advance. This seems to lend a touch of irony under the present circumstances. In any case, while still in Baltimore, I used the method in several projects, including one long forgotten study in which Clay and I[2] demonstrated that, contrary to previous dogma, hypofibrinogenemia need not follow total hepatectomy in dogs if the technique were sufficiently careful.

"We have abandoned our original method, preferring the modification of Ogston, Ogston and Bennett[3] in which the fibrin formed in diluted plasma is caught on a glass cloth filter and is thus more readily washed. Additionally, we form the clot in the presence of 0.005M epsilon-aminocaproic acid, to reduce possible losses from fibrinolysis. More recently, one of my young colleagues, Dr. M. Mortazavi, has found a commercially available, semiautomated adaptation of the method of Ellis and Stransky[4] to be satisfactory, and perhaps more accurate in hypofibrinogenemic states, but this method has not been tested with plasmas containing qualitatively abnormal fibrinogens."

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