The rates of in vivo platelet and fibrinogen destruction were compared in normal subjects and patients showing various consumptive syndromes. Three important patterns emerged. (The SCI® indicates that this paper has been cited in over 495 publications since 1972.)

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April 29, 1985

In the late 1960s, the terms "disseminated intravascular coagulation" or "consumptive coagulopathy" were used as diagnostic terms to include all observed consumptive clinical disorders. Given the wide divergence of syndromes encompassed by this diagnostic term, together with the difficulty of understanding the mechanism from an evaluation of blood levels only, we reasoned that measurements of turnover rates for platelets and fibrinogen should give a rational interpretation of ongoing mechanisms and a prediction of the effects of various antithrombotic therapies. Indeed, the experience in the 35 normal subjects and 104 patients studied provided a useful clinical conceptualization of the pathophysiology underlying these clinical disorders: (1) combined fibrinogen and platelet destruction due to activation of the coagulation system under stagnant flow conditions that is interrupted by anticoagulation; (2) selective platelet destruction due to the interaction of platelets with abnormal endovascular surfaces in high shear settings that responds to treatment with antiplatelet drugs; and (3) selective fibrinogen destruction produced by primary activation of the fibrinolytic system that is normalized by inhibitors of fibrinolysis.

The frequent citation of this paper probably reflects the pathophysiologic characterization of a large number of clinical syndromes by platelet and fibrinogen kinetic measurements. The usefulness of turnover measurements to evaluate rates of destruction was particularly fortunate because it was found to be quantitatively superior to the measurement of circulating concentrations and was, therefore, useful for in vivo evaluation of the effects of therapy. Moreover, the measurement of survival and turnover of platelets and fibrinogen continues to be one of the few valid in vivo approaches in thrombosis to detect patients at risk and to assess therapy objectively. Subsequently, the conclusions from this paper proved helpful in formulating antithrombotic strategies in a broader context.1-3

There are several additional interesting aspects of this publication. First, the availability of a clinical research center in an academic medical center was essential in carrying out these studies. Since patients had to be documented steady-state with respect to platelets and fibrinogen and the kinetic measurements required multiple serial sampling over a 5- to 10-day period of time, and therapeutic intervention required at least an equivalent additional period of study, this work was very time-, resource-, and labor-intensive. The clinical research center provided the only means to accommodate such time-consuming inpatient studies. Second, this seven-page paper represented our total commitment for three full years. Although there were sufficient data included in this work to justify many more publications, we believe that the conceptual formulation was best documented by including all of the data together. It is probably impossible for bench investigators to appreciate the commitment in time and resources represented by these studies. Indeed, in today's climate, we probably could not have survived in research with the publication of a single paper as evidence of three years' effort. Finally, the Journal of Clinical Investigation rejected this paper for publication before it was sent to the New England Journal of Medicine. In retrospect, it is not surprising, since clinical investigation is seldom published in the Journal of Clinical Investigation, despite its title. Perhaps our strategy might be useful for others to consider when responding to the rejection by a premier journal of an important scientific study, namely, resubmit to a journal of equal or higher quality.