The love of the artist for his model of thrombin generation

H. C. HEMKER and S. BÉGUIN

Synapse bv, Cardiovascular Research Institute Maastricht, University of Maastricht, Maastricht, the Netherlands

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Research is an art that by convention we disguise as pure reason. One of the most intuitive—and therefore artistic—aspects of research is the choice of a model. It is one of the most important as well, because that choice determines to a large extent the view of physiological reality that we develop. For many years, for example, platelet reactivity (adhesion, aggregation, Ca2+ influx, etc.) has been mainly studied in anticoagulated blood or in washed platelets. The plasmatic clotting system, on the other hand, has been studied in platelet-poor plasma or on isolated clotting factors.

One tends to become emotionally attached to one’s favorite model and see the whole universe through the window that it opens. For example, the picture of hemostasis in which platelet adhesion and aggregation on the one hand and plasmatic coagulation on the other are represented as isolated functions—as isolated as the laboratories that studied them—has reigned for a long time and has become a textbook paradigm. As soon as we use models in which we allow the platelet and the plasma to meet, it appears that there are many and varied relationships. In the past such studies were scarce but there is a trend for them to become more and more in vogue, consequently our view of what platelets do gradually changes.

In this issue appears an article by one of the pioneer groups exploring this interaction [1]. Allen et al. give an in depth investigation of the dependency of thrombin generation in a cell-based model, i.e. a situation where thrombin is formed on the surface of platelet(aggregate)s and tissue factor bearing monocytes. Their contribution is remarkable not only for its results, but also for the cautious and balanced discussion of the use of model systems. As the authors state, ‘The study of the basic mechanisms of hemostasis is difficult, as is the interpretation of one’s data and extrapolation to the true physiological state. Furthermore, the heterogeneity of the multitude of experimental systems currently in use makes comparison with the findings of other investigators problematic. All experimental systems, whether in vitro, ex vivo or in vivo, are in their own way artificial, with limitations both known and unknown’.

Indeed, thrombin generation in the model presented here differs in several respects from that on the surface of procoagulant microparticles, and the authors conclude that ‘platelets contribute more than simply a surface for the generation of thrombin’.

The main difference appears in the type of response to variations in clotting factor concentrations. In an enzymatic reaction in solution one would expect the rate to be saturable in substrate and proportional to the amount of enzyme. The overall picture that develops from the experiments of Allen et al. is that reaction velocity is linear in substrate (prothrombin) concentration and saturable in the factors that contribute to prothrombinase formation. If we replott their data in terms of molar concentrations rather than as a percentage of the plasma concentration (Fig. 1), this becomes even more obvious.

This phenomenon may be due to specific properties of cell surfaces, as suggested, but it should not escape our attention that the introduction of cell surfaces introduces dimensions that are very large compared with the individual interacting molecules. This introduces (diffusional) transport to the surface.

Correspondence: H. C. Hemker, Synapse b.v. Cardiovascular Research Institute Maastricht (CARIM), POB 6211 LM Maastricht, the Netherlands.
Tel.: +31 43 38816765; fax: +31 43 3884570; e-mail: HC.Hemker@Thrombin.com

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Fig. 1. Relation between clotting factor concentration and rate of thrombin formation. △: factor V; ×: factor VIII; ○: factor IX; ●: factor X; ■: factor XI.
as a complicating factor. This links the present model to others in which prothrombinase is bound to a large surface. The activity of prothrombinase on such ‘macroscopic’ surfaces has been shown to be diffusion limited [2]. This makes it become linear in prothrombin concentration and virtually independent of enzyme concentration, once a low critical limit has been reached: strikingly similar to the results shown by Allen et al. It may therefore well be that the differences observed between the ‘cell-bound’ results and those employing phospholipid vesicles is (partly?) due to a physical reason rather than to a (bio)chemical one.

This is all the more important because, indeed, the use of natural surfaces for the generation of thrombin may be more representative than the use of phospholipid particles. The very fact that the arm–tongue circulation time is of the order of the Quick time shows that thrombin generation in free solution must be of far less physiological importance than surface-bound thrombin generation or thrombin generation in the interior of a platelet aggregate.

Certainly, as stressed by the authors, the nature of such surfaces determines the reactions observed. However, sheer physical size and the diffusion limits that it imposes should also not escape attention as one of the important differences between models.

References