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This Week's Citation Classic®

Hardisty R M & Hutton R A. The kaolin clotting time of platelet-rich plasma: a test of platelet factor-3 availability. *Brit. J. Haematol.* **11**:258-68, 1965.
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A method is described for measuring the contribution of platelet membrane phospholipid to blood coagulation (platelet factor-3 availability), based on the kaolin clotting time of platelet-rich plasma. The induction of this activity by kaolin is deficient in thrombasthenia and blocked by ADP inhibitors. [The *SCI*® indicates that this paper has been cited in over 220 publications.]

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In the early 1960s, when a powerful platelet-aggregating agent from red cells had just been identified as ADP and when platelet aggregometry was in its infancy, the classification of hereditary disorders of platelet function was in disarray. The late Katharine Dormandy, Ron Hutton, and I, on the basis of our studies on three patients at the Hospital for Sick Children, Great Ormond Street, London, proposed that the term "thrombasthenia" should be redefined as a hereditary platelet defect resulting in a complete failure to aggregate in response to ADP[1]—a definition that still holds good, though more recent work in Paris and elsewhere has uncovered the molecular basis for the disorder. In order to study the procoagulant function of these patients' platelets, Ron and I devised the very simple test, which we subsequently described in detail in this paper, to avoid artifacts due to the *in vitro* damage to platelets inflicted by previous methods.

As it happens, this paper bears a double similarity to my previous *Citation Classic*[2] in that it describes a method based on the kaolin clotting time and that a very similar method was independently developed at the same time by one of my American friends. It was, in fact, on the boardwalk at Atlantic City in 1964 that Ted Spaet and I discovered that we had—not for the first time—been working along very similar lines, and we decided to submit our papers to the *British Journal of Haematology* as a pair. His method[3] differed chiefly in its use of Russell's viper venom to activate factor X, whereas ours depended on the kaolin to activate the intrinsic coagulation pathway as well as the platelets. While Spaet and Cintron's method, therefore, provided a specific assay of the accelerating effect of available platelet phospholipid on the conversion of prothrombin to thrombin by factor Xa, ours was also sensitive to the rate of factor X activation by factor IXa, which is equally dependent on the availability of phospholipid. Peter Walsh[4] subsequently provided evidence that these two reactions were dependent on different platelet membrane determinants.

We subsequently adapted Spaet and Cintron's method to study the relationship between platelet aggregation and platelet factor-3[5] and concluded that the latter became available on the platelet membrane as a result of the former. The later work of Zwaal and his collaborators[6] has shown the basis of this membrane change to be the redistribution of specific phospholipids between the inner and outer leaflets. Because the results of our test thus seemed chiefly to reflect platelet aggregability, for the measurement of which more direct methods had become available, we have made little subsequent use of it. It appears from the "classic" status that our paper has achieved that others have found it of more lasting value.

1. **Hardisty R M, Dormandy K M & Hutton R A.** Thrombasthenia. Studies on three cases. *Brit. J. Haematol.* **10**:371-89, 1964. (Cited 145 times.)
2. **Hardisty R M & Macpherson J C.** A one-stage factor VIII (antihaemophilic globulin) assay and its use on venous and capillary plasma. With a note on the calculation of confidence limits by G.I.C. Ingram. *Thromb. Diath. Haemorrh.* 7:215-29, 1962. [See also: **Hardisty R M.** Citation Classic. *Current Contents/Clinical Practice* 9(18):16, 4 May 1981.]
3. **Spaet T H & Cintron J.** Studies on platelet factor-3 availability. *Brit. J. Haematol.* **11**:269-75, 1965. (Cited 225 times.)
4. **Walsh P N.** Different requirements for intrinsic factor-Xa forming activity and platelet factor-3 activity and their relationship to platelet aggregation and secretion. *Brit. J. Haematol.* **40**:311-31, 1978.
5. **Hardisty R M & Hutton R A.** Platelet aggregation and the availability of platelet factor 3. *Brit. J. Haematol.* **12**:764-76, 1966. (Cited 145 times.)
6. **Zwaal R F A, Comfurius P & van Deenen L L M.** Membrane asymmetry and blood coagulation. *Nature* **268**:358-60, 1977. (Cited 65 times.)

