

Citation Classics

Born, Gustav V R. Aggregation of blood platelets by adenosine diphosphate and its reversal. *Nature* 194:927-9, 1962.

A photometric method is introduced with which platelet aggregation and its inhibition by ADP and related compounds respectively are investigated quantitatively. [The SC[®] indicates that this paper was cited 681 times in the period 1961-1975.]

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"To be told that the paper on platelet aggregation I wrote fifteen years ago is 'one of the most cited articles ever published' is astonishing and interesting. I can think of three possible reasons. First, the paper helped to make platelets interesting research objects by suggesting functions for two, then recent, observations which had been made independently but seemed to be related. I found platelets to contain extraordinarily high concentrations of ATP, some of which broke down during clotting. Hellem and colleagues discovered the highly specific induction of platelet aggregation by ADP which is, of course, the first breakdown product of ATP. The paper suggests that these processes are connected through the formation of ADP from ATP in cells damaged by or involved in vascular injury. My current comment would be that that has turned out to be an oversimplification as far as the platelets themselves are concerned, which release ADP mostly from a different pool than that in which ATP breakdown occurs. On the other hand, in spite of much new knowledge about the role of prostaglandins and other endogenous agents in platelet aggregation, much evidence supports the original proposition that ADP formed from ATP in other cells, including red cells,¹ initiates platelet aggregation in the circulation, including that through artificial organs.²

"Secondly, the paper introduced the photometric method which later acquired the

horrible name of 'aggregometry,' whereby it became possible to quantify and analyse platelet reactions *in vitro*. Not long before I had been following ribonuclease activity 'turbidimetrically' and I simply made the banal adaptations appropriate for measuring changes in light transmission associated with the aggregation of platelets in plasma. For some time the measurements remained wholly empirical; then the relation between the optical and the cellular events was established and quite recently the optical observations have been explained on the basis of light-scattering theory.³

"Already before publication the photometric method was rapidly taken up by visitors to whom it had been demonstrated; and after the paper appeared 'aggregometry' soon became widely used, presumably because of its simplicity and reproduceability. It has been responsible for major discoveries in platelet function, notably the 'second wave' of aggregation. This is the optical manifestation of the platelet 'release reaction,' much investigated since as an example of exocytosis and because the discovery of its inhibition by acetyl salicylic acid is the origin of the Aspirin trials in coronary thrombosis.

"This brings up the third reason for the popularity of the 1962 paper. It showed that platelet aggregation by ADP can be inhibited and reversed by the closely related substances AMP or ATP. The last paragraph of the paper reads: 'If it can be shown that ADP takes part in the aggregation of platelets in blood vessels it is conceivable that AMP or some other substance could be used to inhibit or to reverse platelet aggregation in thrombosis.' Cross and I soon found that AMP was much less inhibitory than adenosine which, in turn, is much less effective than several inhibitors unrelated to ADP which have been discovered since, such as some prostaglandins. Elucidation of these inhibitory mechanisms has made rapid progress, not only because platelets are advantageous models for other cell systems but also because it may result in important advances in drug treatment. I am glad to have contributed to this."

1. **Born G V R, Bergquist D & Arfors K E.** Evidence for inhibition of platelet activation in blood by a drug effect on erythrocytes. *Nature* 259:233-5, 1976.
2. **Richardson P D, Galletti P M & Born G V R.** Regional administration of drugs to control thrombosis in artificial organs. *Transactions of the American Society of Artificial Internal Organs* 22:22-9, 1976.
3. **Latimer P, Born G V R & Michal F.** Applications of light-scattering theory to the optical effects associated with the morphology of blood platelets. *Archives Biochemistry & Biophysics* 180:151-9, 1977.