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Born G V R & Cross M J. The aggregation of blood platelets. *J. Physiology* 168:178-95, 1963.

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This paper describes a turbidimetric method for following quantitatively the aggregation of blood platelets *in vitro*. The effect of calcium chloride and adenosine diphosphate (ADP) on aggregation of platelets was measured. Adenosine and its monophosphate inhibit aggregation by ADP. [The *SCI*® indicates that this paper has been cited in over 1,295 publications.]

Platelet Aggregometry Is 25 Years Old

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That the paper of just over 25 years ago, with my late and greatly missed coworker and friend Michael J. Cross, has remained one of the most-cited publications in its field is, of course, a satisfying outcome of the work we did so long ago. It is all the more gratifying because this paper is a fuller sequel to my *Nature* paper on platelet aggregation, which appeared a few months earlier and itself became a *Citation Classic*.[1] This was, therefore, the second publication, other than printed communications to the Physiological Society, in the series that established the fundamental features of platelet aggregation *in vitro*. These have turned out to be correct if not complete descriptions of the process *in vivo*, where it is at the origin of coronary and cerebral thromboses and therefore of tremendous importance in clinical medicine.

Michael joined me for utilising the new method of optical aggregometry, introduced in the preceding paper, for establishing the basic properties and limitations of the method, which are described in this paper. That was before we acquired a pen recorder, so that successive measurements of light transmissions through platelet-rich plasma were read on the galvanometer and plotted on graph paper. The preceding paper had already described the inhibitory effect of adenosine triphosphate (ATP) on aggregation induced by adenosine diphosphate (ADP), just then discovered by the Norwegians.[2] Our paper brought the discovery of the much more potent inhibitory effect of adenosine on aggregation. It took several years of further work by others as well as by ourselves to establish that inhibition by ATP was competitive at the ADP receptor whereas that by adenosine was through the adenosine 3',5' monophosphate mechanism. These observations showed that platelet aggregation could be specifically and potently inhibited. Thereby the principle was established that ultimately led to the many clinical trials, not yet concluded, of aspirin as an inhibitor of platelet thrombus formation in the prevention of myocardial and cerebral infarction.

That we were already thinking about the possible physiological significance of all this is shown by the last paragraph of the discussion: "It is difficult to think of any physiological significance of this [platelet aggregating] effect of ADP in red cells, except perhaps in the spleen. There are reasons for believing that red cells and platelets end their existence in the spleen. It is, therefore, possible that ADP released from red cells disintegrating in the spleen causes the circulating platelets to aggregate there and so to become trapped and to disintegrate in their turn." To the best of my knowledge this, like so much else, still awaits experimental confirmation or refutation. It is comforting that, in spite of the explosion of platelet research since then, many fundamental uncertainties remain.

What is now quite certain is that platelet aggregation initiates coronary thrombosis in consequence of haemorrhage into fissured atheromatous plaques. The cause(s) of plaque fissuring, so far unknown, is now being investigated by M.J. Davies, P.D. Richardson, and me.[3] Because the clinical importance of platelets would be greatly diminished if the problem of atherosclerosis were resolved, I am also working on atherogenesis. Recently, Noel J. Cusack, Shahida Shafi, and I have obtained evidence that noradrenaline in low concentrations accelerates the atherogenic uptake of low-density lipoprotein from blood into arterial walls in anaesthetised rabbits.[4] If noradrenaline has a similar effect in man, it would suggest an explanation for the accelerated atherosclerosis and the increased incidence of its clinical manifestations, predominantly myocardial infarction, in conditions associated with increased blood noradrenaline concentrations such as cigarette smoking and continued stress.

1. **Born G V R.** Aggregation of blood platelets by adenosine diphosphate and its reversal. *Nature* 194:927-9, 1962. (Cited 2,435 times.) [See also: **Born G V R.** Citation Classic. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 2: the molecules of life.* Philadelphia: ISI Press, 1986. p. 80.]
2. **Gaarder A, Jonsen J, Laland S, Hellem A & Owren P A.** Adenosine diphosphate in red cells as a factor in the adhesiveness of human blood platelets. *Nature* 192:531-2, 1961. (Cited 685 times.)
3. **Richardson P D, Davies M J & Born G V R.** The pathogenesis of fissuring in human atherosclerotic plaques. (In press.)
4. **Shafi S, Cusack N J & Born G V R.** Increased uptake of methylated low-density lipoprotein induced by noradrenaline in carotid arteries of anaesthetised rabbits. *Proc. Roy. Soc. London Ser. B* 235:289-98, 1989.

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