

This Week's Citation Classic

Mitchell J R A & Sharp A A. Platelet clumping *in vitro*. *Brit. J. Haematol.* 10:78-93, 1964.
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The ability of 5HT and the adrenalines to aggregate platelets was described and the dependence of aggregation on movement and collision emphasized. The reversibility of aggregation and its relationship to calcium and magnesium ions, and therefore to the anticoagulant used, was shown, as was the affinity of polymorphs for growing platelet aggregates. Finally, the value of enzyme poisons and receptor blockers as tools in platelet research was outlined. [The SC® indicates that this paper has been cited in over 295 publications since 1964.]

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"An occupational disease of authors is a morbid fear that their imperishable words will never be read, so it is pleasant to find that our 1964 paper has been widely cited. It represented the second step in the recognition that some simple and universally distributed chemical substances, unrelated to blood-clotting factors, could activate platelets. The first step was the revelation by Hellem and his Oslo colleagues that ADP was an aggregating agent.¹ We asked ourselves whether the presence of large amounts of ADP in platelets provided a self-amplifying system whereby aggregation would release more ADP which would then promote further aggregation. We decided to see whether other materials stored within platelets could do the same trick and in January 1962 found that 5HT and the adrenalines were active platelet aggregating agents.

"One of our colleagues at that time was editor of the *British Journal of Haematology* so we were urged to publish our findings therein. To our dismay, we found that although we had

been presenting our work at meetings, a backlog of papers meant that ours would not appear until 1964. This prevented workers who were using 5HT and the adrenalines from referring to our work. At that time we were working in the haematology department of the Radcliffe Infirmary, Oxford, with that most imaginative and creative scientist, Cwyn Macfarlane. He had come back from a Vienna congress with the news about ADP so his was the match that lit the fuse. Alan Sharp was a member of his staff, and had previously worked on platelet aggregation in response to thrombin. I was a cardiovascular physician who had been seconded from Sir George Pickering's department to undertake a massive postmortem study of vascular disease with Colin Schwartz.² This had shown the key role of thrombosis in stroke and heart attack, so I had moved on to work on thrombosis with Macfarlane. We worked in a basement at the Radcliffe Infirmary (which regularly flooded when the River Thames rose) with our assistants, Sheila Briers and Margaret Eggleton.

"Our work has been widely cited because, as well as the identification of 5HT and the adrenalines, it showed that aggregation was a reversible process, that the agents did not pull platelets together, but allowed them to adhere when movement produced collision, and that polymorphs adhered to platelet clumps. We also documented the crucial role of calcium and magnesium ions and of the anticoagulant chosen for studies. We did not understand the nature of the forces which produced aggregation nor how these forces could be negated to allow disaggregation. I still cannot answer these questions and I know that no one else can either. This is why, when I moved to my present position as Foundation Professor of Medicine in the new University of Nottingham Medical School in 1968, I built up an active platelet/thrombosis team headed by Stan Heptinstall, and we are still trying to answer the same questions."^{3,4}

1. Gaarder A, Jonsen J, Laland S, Hellem A J & Owren P A. Adenosine diphosphate in red cells as a factor in the adhesiveness of human blood platelets. *Nature* 192:531-2, 1961.
2. Mitchell J R A & Schwartz C J. *Arterial disease*. Oxford: Blackwell Scientific, 1965. 411 p.
3. White A M & Heptinstall S. Contribution of platelets to thrombus formation. *Brit. Med. Bull.* 34:123-8, 1978.
4. Mitchell J R A. Prostaglandins in vascular disease; a seminal approach. *Brit. Med. J.* 282:590-4, 1981.