CC/NUMBER 51
DECEMBER 22,1980

This Week's Citation Classic

O'Brien J R. Effects of salicylates on human platelets. *Lancet* **1:**779-83, 1968.
[Portsmouth and Isle of Wight Area Path. Serv., Portsmouth, Hampshire, England)

When studying the aggregation of platelets, I found that the ingestion of aspirin produced an abnormal response which was dose related and lasted for days. I concluded that aspirin, possibly permanently, damages a platelet mechanism probably related to release of ADP. [The *SCI*® indicates that this paper has been cited over 375 times since 1968.]

J. R. O'Brien
Hampshire District Pathology Service
Saint Mary's Hospital
Portsmouth PO3 6AG
England

November 13, 1980

"As usual I was not really first in the field. There are few real beginnings in science. It usually grows and evolves in an appropriate climate. Mustard[1] had studied anti-in-flammatory drugs in animals and Marjorie Zucker[2] had studied a normal volunteer who always had headaches and abnormal platelet responses and was a constant aspirin eater. Also, Weiss[3] had already reported some aspirin effects. The aggregometer principle applied to platelets by Born[4] and myself[5] simultaneously gave a tremendous stimulus to platelet 'phenomenology' and the aspirin effect on platelet aggregation was an early and important one. Aggregation phenomena were so exciting that I almost believe it delayed other studies of platelets *in vivo* and the search for more meaningful tests. Indeed aggregation studies still are of limited clinical application.

"Aspirin had always fascinated me. The drug has so many different effects —anti-inflammatory, analgesic, influencing red cell membranes, etc. There had to be some common factor. And now in 1968, aspirin was found to influence platelets as well and in a dose far smaller than that influencing any other identified physiological system. And aspirin was known to prolong the bleeding time. Being no chemist, I could not contribute to the unravelling of the prostaglandin story. But this paper may have helped others.

"In this paper I do not specifically discuss 'aspirin labelling' as a method of measuring the rate of platelet regeneration, but I did suggest that megakaryocytes were also damaged. Thus to an extent, the 'platelet regeneration time' (now usually monitored by the reappearance of malondialdehyde production, a biproduct of prostaglandin synthesis) may be said to have in part been initiated by this paper; however, the megakaryocyte labelling, if it occurs, is still at least a theoretical objection to this method.

"In 1963, I published a paper entitled, An *in vivo* trial of an anti-adhesive drug'[6] which I think was the first paper with the acknowledged aim of developing an anti-platelet drug to prevent thrombosis. So in 1968 when aspirin was known to prolong the bleeding time and to influence platelets, it was only reasonable to speculate that it might prevent thrombosis by virtue of its 'anti-platelet' activity. This was a far cry from the current complexity of platelet cyclooxygenase inhibition and the additional effect on vessel wall prostacyclin synthesis which may or may not be relevant to any anti-thrombotic effect which finally emerges. Nevertheless this paper contributed to the concept that antiplatelet drugs might be used to prevent thromboses.

"I am a full-time haematologist and did not carry out manually any of these experiments; S. Shoobridge, W. J. Finch, and J. Dore did all the work, but I ate much of the aspirin and salicylates—once until I got tinnitus which to my alarm continued for six weeks after stopping the drug!

"It was an exciting, happy time with new and usually quite unexplained phenomena occurring every few months. Was this the golden age for platelets? Or is this selective gilded memory looking back 12 years?"

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2. **Zucker M B & Peterson J.** Inhibition of adenosine diphosphaie-induced secondary aggregation and other platelet functions by acetylsalicylic acid ingestion. *Proc. Soc. Exp. Biol. Med.* **127:**547-51. 1968.
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4. **Born G R V.** Aggregation of blood platelets by adenosine diphosphate and its reversal. *Nature* **194:**927-9, 1962.
5. **O'Brien J R.** Some results from a new method of study. Pan II. J. *Clin. Pathol.* **15:**452-5. 1962.
6. **.....** An *in vivo* trial of an anti-adhesive drug. *Thromb. Diath. Haemorrh.* **9:**120-5. 1963.