CC/NUMBER 18
APRIL 30, 1984

This Week's Citation Classic ™

Moncada S, Gryglewski R, Bunting S & Vane J R. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature* **263**:663-5, 1976.
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This work describes the discovery of PGX, a powerful vasodilator and inhibitor of platelet aggregation, generated by vascular tissue The potential biological importance of this compound is related to the homeostatic regulation of platelet vessel wall interactions (The *SCI*® indicates that this paper has been cited in over 1.32S publications since 1976.]

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March 7, 1984

"The period comprising the summer, autumn, and winter of 1975/1976 was one of the most exciting times in the life of our laboratory' in Beckenham. We had been chiefly dedicated to work on inflammation for several of the preceding years, but in July 1976 at the International Congress on Prostaglandins in Florence, Bengt Samuelsson announced the structure of the elusive rabbit aorta contracting substance (RCS) described by Piper and John Vane in 1969.[1] That compound, which was released from lungs and from platelets, was renamed thromboxane A_2 and its most important biological activities were its vasoconstrictor and pro-aggregating actions. We decided to look for the enzyme responsible for the transformation of the prostaglandin endoperoxides into thromboxane A_2. This led, in a short period, not only to the isolation and partial characterization of an enzyme which we named 'thromboxane synthetase,' but also to the development of bioassay tissues capable of detecting unstable substances, which were to be so important in the discovery of prostacyclin. In addition to the rabbit aortic strip which had been used in cascade superfusion by Piper and Vane for the discovery of RCS, we started to prepare, with Stuart Bunting, strips of the coeliac and mesenteric arteries of the rabbit, which differentiated between the prostaglandin endoperoxides and thromboxane A_2. An important addition to this dynamic bioassay system was the inclusion of studies of platelet aggregation. During that time, we also found the first specific inhibitors of thromboxane synthetase.

"Our intention was to continue this work and, as Vane put it, to 'map the body' for sites of thromboxane A_2 synthesis. I was especially interested in reexamining the metabolism of arachidonic acid in the vessel wall. The reason for this was twofold. First, I had recently been impressed by an article by Morrison and Baldini[2] showing that platelets and the vessel wall share some common proteins, and, second, recent results in our laboratory measuring cutaneous bleeding time in the rat had shown very erratic results which needed explanation. My hypothesis was simple, namely, that thromboxane A_2 generated by the vessel wall might synergize with thromboxane A_2 synthesized by the platelets, for the formation of the haemostatic plug. In autumn 1975, Richard Cryglewski joined us for a six-month sabbatical from Krakow University, and we searched for generation of thromboxane in many tissues, especially the vessel wall.

"Our results were disappointing. We could not find other tissues like the platelets which were able to produce large quantities of bioassayable thromboxane A_2. For the vessel wall, too, an enzyme preparation made from pig aortae obtained from a local abattoir failed to generate thromboxane A_2. When a second experiment was done, after another disappointing day, we noticed that something unexpected was happening: although thromboxane A_2 was not formed, the precursor used in the reaction, the prostaglandin endoperoxide, seemed to disappear. After looking at the results of the experiment, I suggested two further experiments to distinguish between simple inactivation of the endoperoxides and the possibility that a new active substance was being formed which our bioassay tissues did not detect. These experiments showed that indeed we had discovered a new metabolic pathway which produced an unstable substance which relaxed the strips of mesenteric and coeliac arteries. We called this substance PGX.

"The next important step came several weeks later when it occurred to me that since we had been looking for thromboxane A_2, which was a vasoconstrictor and aggregator of platelets, and we had found instead a vasodilator, the equation would be completed if the newly found substance also inhibited platelet aggregation. On that day, which was probably the most exciting for me in the whole process of discovery because it gave a clear idea of the biological implications of this compound, we found that PCX was a strong inhibitor of platelet aggregation. Later developments have demonstrated that prostacyclin has not only physiological importance, but also that its absence might underlie some pathological conditions such as atherosclerosis. It is also likely that prostacyclin will provide the basis for the development of potent antithrombotic compounds. The discovery of prostacyclin has increased our understanding of those aspects of the cardiovascular system concerning the interaction between platelets and the vessel wall. For a recent review, see reference 3."

1. **Piper P J & Vane J R.** Release of additional factors in anaphylaxis and its antagonism by anti-inflammatory drugs. *Nature* (London) **223**:29-35, 1969. (Cited 640 times .)
2. **Morrison F S & Baldini M G .** Antigenic relationship between blood platelets and vascular endothelium. *Blood* **33**:46-57, 1969.(Cited 35 times.)
3. **Moncada S,** ed. Prostacyclin. thromboxane and leukotrienes.(Whole issue.) *Brit. Med. Bull.* **39**(3), 1983, 91 p.