

Moncada S, Higgs E A & Vane J R. Human arterial and venous tissues generate prostacyclin (prostaglandin X), a potent inhibitor of platelet aggregation. *Lancet* 1:18-21, 1977.
[Wellcome Research Labs., Beckenham, Kent, England]

Human arterial and venous tissues generate prostacyclin, an unstable substance which potently inhibits platelet aggregation. Prostacyclin synthesis is inhibited by 15-hydroperoxy arachidonic acid, a lipid hydroperoxide. These suggest that prostacyclin plays a role in preventing platelet aggregation on the vessel wall. Inhibition of prostacyclin synthesis by lipid peroxides may contribute to the genesis of certain diseases. [The *SC*[®] indicates that this paper has been cited in over 475 publications since 1977.]

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"The discovery of prostacyclin in 1976¹ and a series of later papers, published both from our laboratory and in collaboration with the scientists of the Upjohn Company, created the background for the demonstration of the synthesis and release of prostacyclin by human vascular tissue. We had been trying to demonstrate the synthesis of thromboxane A₂ (TXA₂), a powerful vasoconstrictor and inducer of platelet aggregation by the vessel wall, following my hypothesis that its generation in the vasculature might synergise with platelet-derived TXA₂ in the formation of the haemostatic plug. We showed instead that the vessel wall converts arachidonic acid into a powerful vasodilator and inhibitor of platelet aggregation, prostacyclin. The demonstration of the existence of such a compound in human vessels was of obvious interest and excitement. Prostacyclin is the biological counterpart of TXA₂. We have suggested that a balance between these two compounds plays a role in the control of platelet aggregation *in vivo* and that some of the thromboresistant properties of the vascular endothelium might be related to prostacyclin generation. Some of our hypotheses are at present being studied and it will probably be

some time before elucidation of the biological role of prostacyclin is made.

"Some pathological conditions have been associated with a decrease in prostacyclin formation. The most striking is the association between the vascular complications of diabetes and a reduced prostacyclin generation; such a reduction has also been implicated in atherosclerosis. As yet, research into the possible role of lipid peroxides (strong inhibitors of prostacyclin formation^{2,3}) in the development of atherosclerosis is just beginning. This promises to be a fascinating area of research.

"While basic and clinical research continues, synthetic prostacyclin has been successfully used clinically in a number of conditions. These include situations in which the blood has to be exteriorized from the body, such as cardiopulmonary bypass operations, renal dialysis, and charcoal haemoperfusion. Other conditions such as peripheral vascular disease, Reynaud's syndrome, pre-eclampsia, and thrombotic thrombocytopenic purpura are being studied intensively.

"Prostacyclin has also provided a naturally occurring molecule which comprehensively inhibits platelet aggregation. It is highly likely that new inhibitors of platelet aggregation, based on the chemical structure of prostacyclin, will be developed, probably orally active and long lasting. These compounds will have a superior antiplatelet activity to those available at the moment and, therefore, will allow more comprehensive study and better treatment of thrombotic disease.

"Looking back at January 1977, I would say that this paper aroused so much interest because human tissue was used, giving a 'degree of respectability' to the discovery of prostacyclin. Five years later, I think prostacyclin has already established itself as an endogenous substance to be 'reckoned with' if one wants to understand platelet/vessel wall interactions. As very often happens, thinking back to that time, I find myself wondering how it happened that prostacyclin was there for so long but nobody saw it before us."

1. **Moncada S, Gryglewski R J, 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.
2. A lipid peroxide inhibits the enzyme in blood vessel microsomes that generates from prostaglandin endoperoxides the substance (prostaglandin X) which prevents platelet aggregation. *Prostaglandins* 12:715-33, 1976.
3. **Salmon J A, Smith D R, Flower R J, Moncada S & Vane J R.** Some characteristics of the prostacyclin synthesizing enzyme in porcine aorta. *Biochim. Biophys. Acta* 523:250-62, 1978.