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Hamberg M & Samuelsson B. Prostaglandin endoperoxides. Novel transformations of arachidonic acid in human platelets. *Proc. Nat. Acad. Sci. US* 71:3400-4, 1974.
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Arachidonic acid added to human blood platelets is transformed by two dioxygenase pathways, i.e., one initiated by fatty acid cyclo-oxygenase and another initiated by arachidonic-acid-12-lipoxygenase. The structures of three major end-products are described. [The *SCI*® indicates that this paper has been cited in over 900 publications since 1974.]

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"In 1972-1973, we isolated and characterized two unstable endoperoxide intermediates in prostaglandin biosynthesis, i.e., prostaglandins G_2 and H_2.[1,2] The endoperoxides proved to be potent stimulators of vascular and respiratory smooth muscle.[1-3] We were also interested in examining the possible effects of endoperoxides on blood platelets. Platelets have a contractile system and in many respects may be looked upon as a smooth-muscle tissue. At that time, the role of prostaglandins in platelet function was poorly understood. In fact, a paradoxical situation existed since a) prostaglandins had been found to be mainly anti-aggregative agents and b) aspirin and other nonsteroidal anti-inflammatory drugs, inhibitors of prostaglandin biosynthesis,[4] were known to inhibit platelet aggregation and to increase the bleeding time. Thus, if prostaglandins played a role in platelet aggregation, it would be logical to expect them to have a pro-aggregative effect rather than anti-aggregative. We will never forget the day when we prepared a suspension of human platelets, added pure prostaglandin H_2, and found that this endoperoxide indeed caused platelet aggregation. The same was true for prostaglandin G_2, although this endoperoxide was somewhat more potent. The finding that the cyclo-oxygenase system of platelets has a pro-aggregative role initiated further work on the mechanism of action, analogs, inhibitors, and so on. It seemed important next to investigate the capacity of human platelets to synthesize endoperoxides and to study the further metabolism of endoperoxides in platelets. We chose ^{14}C-arachidonic acid for this task since this fatty acid is the predominant cyclo-oxygenase substrate present in platelet lipids.

"Three major stable end-products formed from arachidonic acid by two pathways were isolated and characterized. Two compounds, i.e., thromboxane B_2 (provisionally called 'PHD') and 12L-hydroxy-5,8,10-heptadecatrienoic acid (12-HHT) were formed by reactions initiated by fatty acid cyclo-oxygenase. As expected, formation of these products was inhibited by aspirin and related drugs. The third compound, 12L-hydroxy-5,8,10,14-eicosatetraenoic acid (12-HETE), was formed by a pathway initiated by arachidonic-acid-12-lipoxygenase. This enzyme was not inhibited by aspirin but by several antioxidant drugs and by 5,8,11,14-eicosatetraynoic acid. An interaction between the lipoxygenase and cyclo-oxygenase pathways in platelets has been found; however, the exact biological role of 12-HETE and its hydroperoxide precursor remains unclear.

"We think the reasons for the high citation rate of this study are a) the discovery of a true lipoxygenase in mammalian tissue, inspiring further studies on transformations of polyunsaturated fatty acids by mammalian lipoxygenases[5] and b) the isolation of thromboxane B_2, which subsequently led to the detection of thromboxane A_2, an unstable, extremely potent aggregating agent in platelets."[6]

1. **Hamberg M & Samuelsson B.** Detection and isolation of an endoperoxide intermediate in prostaglandin biosynthesis. *Proc. Nat. Acad. Sci. US* 70:899-903, 1973. (Cited 540 times.)
2. **Hamberg M, Svensson J, Wakabayashi T & Samuelsson B.** Isolation and structure of two prostaglandin endoperoxides that cause platelet aggregation. *Proc. Nat. Acad. Sci. US* 71:345-9, 1974. (Cited 855 times.)
3. **Hamberg M, Hedqvist P, Strandberg K, Svensson J & Samuelsson B.** Prostaglandin endoperoxides IV. Effects on smooth muscle. *Life Sci.* 16:451-62, 1975. (Cited 195 times.)
4. **Vane J R.** Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature New Biol.* 231:232-5, 1971. [See also: **Vane J R.** Citation Classic. *Current Contents/Life Sciences* 23(42):12, 20 October 1980.]
5. **Samuelsson B.** Leukotrienes: mediators of immediate hypersensitivity reactions and inflammation. *Science* 220:568-75, 1983.
6. **Hamberg M, Svensson J & Samuelsson B.** Thromboxanes: a new group of biologically active compounds derived from prostaglandin endoperoxides. *Proc. Nat. Acad. Sci. US* 72:2994-8, 1975. [See also: **Hamberg M.** Citation Classic. *Current Contents/Life Sciences* 26(2):19, 10 January 1983.]