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This Week's Citation Classic

Vane J R. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature New Biol.* **231**:232-5, 1971.
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The generation of prostaglandins by a cell-free enzyme preparation *in vitro* was measured by bioassay. Aspirin-like drugs inhibited the formation of prostaglandins. This enzyme inhibition was proposed as the mechanism of therapeutic action and side effects of aspirin-like drugs, implicating prostaglandins in inflammation. [The *SCI*® indicates that this paper has been cited over 1,915 times since 1971.]

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"The aspirin-like drugs are not only amongst the most widely used synthetic Pharmaceuticals but also amongst the oldest. Even so, there was no widely accepted theory to explain their actions. The drugs' three salient properties – anti-pyresis, anti-inflammation, and analgesia– seemed unrelated to one another as did their shared side effects.

"The discovery that aspirin and similar compounds prevented the biosynthesis of prostaglandins (PGs) suggested that this enzyme inhibition accounted for their therapeutic effects. It came at a time when interest was burgeoning in prostaglandins, which had already been detected in inflammatory exudates and shown to mimic some of the signs and symptoms of inflammation.

"The finding was a consequence of our development of a method of parallel bioassay which allowed the immediate and continuous detection of the release of vasoactive substances, such as histamine, serotonin, epinephrine, bradykinin, and some of the PGs. The method had the advantage of simplicity and allowed the maximum opportunity for serendipity. We were using this technique to study the release from lungs of putative mediators of anaphylaxis, and found some unexpected ones – PGE_2, $PGF_{2\alpha}$and an ephemeral substance which we called 'rabbit aorta contracting substance' or RCS. Aspirin abolished the output of RCS (nowadays known as thromboxane A_2). Later experiments using a different system showed that aspirin also abolished the release of PGs. Whilst working on a review over the weekend, I realized that stimulated tissues released more PGs than they contained, equating release with stimulation of biosynthesis. Could aspirin be preventing PG biosynthesis? On that Monday morning I said to my colleagues, 'I think I know how aspirin works.' I told them my hypothesis and set about experimenting to put it to the test. The most direct test of whether aspirin inhibited prostaglandin biosynthesis was to make an *in vitro* preparation of the enzyme involved. As a classical pharmacologist, I had always been taught to study whole tissues, rather than smash them into bits. However, I found a paper describing prostaglandin synthetase made from homogenised lungs[1] and on that same day made my very first enzyme preparation. It worked, and so did aspirin as an inhibitor!

"The forging of the aspirin-prostaglandin link was important for several reasons. First, it established a scientifically satisfactory mode of action for aspirin-like drugs, now generally accepted. Secondly, it provided a simple enzyme test for discovering new, and hopefully better, aspirins. Thirdly, it provided a tool by which biologists could study the importance of prostaglandins in the body's processes. Give an aspirin-like drug, see what it does to a particular organ or function and that tells you what a lack of prostaglandins does. Fourthly, from the elucidation of the role of prostaglandins in the body, it suggested new uses for aspirin-like drugs."

1. **Anggård K & Samuelsson B.** Biosynthesis of prostaglandins from arachidonic acid in guinea pig lung. *J. Biol. Chem.* **240**:3518-21, 1965.