

Ferreira S H & Vane J R. Prostaglandins: their disappearance from and release into the circulation. *Nature* 216:868-73, 1967.

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The blood-bathed organ technique was used to detect and continuously estimate the concentration of prostaglandins E_1 , E_2 , and $F_{2\alpha}$ in the circulation, to determine their stability in the blood and their disappearance in different vascular beds. Prostaglandins are released into the splenic venous blood during spleen contractions. The pulmonary circulation provides an efficient protective mechanism for it removes almost all the prostaglandins before they reach the arterial circulation. [The SC¹⁹ indicates that this paper has been cited in over 745 publications since 1967.]

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"In previous papers, we investigated the disappearance of peptides and amines^{1,2} in the circulation and realized the usefulness of the blood-bathed organ technique for measuring the metabolism of biologically active substances in blood or during a single passage through a vascular bed. The present study with prostaglandins started as a sequel to our paper on bradykinin.¹ We developed a set of bioassay tissues for measuring certain prostaglandins in the circulating blood and applied it for detecting this substance after endogenous release or after removal in various vascular beds. At that time, we had just received from Upjohn samples of the precious synthetic prostaglandins E_1 , E_2 , and $F_{2\alpha}$. I remember Vane asking me to investigate the fate of angiotensin I in the pulmonary circulation as well as the action of the peptide extracts from the venom of *Bothrops jararaca* which I had brought with me. This preparation, the bradykinin potentiating factor (BPF), was known to inhibit inactivation of bradykinin and potentiate its effect. I had been working mostly with peptides since my initial research training in Brazil with Rocha e Silva and I decided then to work with prostaglandins in order to get some experience with another class of substances. In consequence, I missed the opportunity of discovering the role of

the lung in the conversion of angiotensin I and of the snake venom peptides as inhibitors of converting enzyme.^{3,5}

"I believe that our prostaglandins paper became a *Citation Classic*™ because the experiments led to the right results, being made at the right time and at the right place. In fact our results were soon confirmed by various groups using different techniques. The time was right because it coincided with the beginning of the explosive development of the prostaglandin field.

"Was Vane's laboratory the right place? While the experiments were being carried out we realized the importance of the lung as a metabolic organ. Placed at a very strategic position in the circulatory system, the lung could control the arterial level of circulating substances. A substance which escaped pulmonary clearance might be a systematic mediator, while those removed by the lungs might play a role only as local hormones. Thus, our descriptive paper led to a new concept and Vane geared his group to test this hypothesis. In a short time, the importance of the lungs as a filter was established allowing passage of some endogenous mediators but removing others.⁴ The groups also found that with certain provoking stimuli, the lungs could release a novel substance (RCS) which was able to contract the isolated rabbit aorta.⁶ The activity of RCS was later shown to be due to thromboxane A_2 . It was by the inhibition of the generation of prostaglandins in lung homogenates and of the release of prostaglandins by spleen that the mode of action of aspirin-like drugs was established.^{7,9}

"Some papers become 'instant' classics either due to their relevance, as a missing piece in the biological puzzle, or because they describe a new practical research tool. This paper fits in neither group in my opinion. But those first papers on the disappearance of bradykinin and prostaglandins played a strongly stimulating role in Vane's laboratory. However, bradykinin was losing momentum and prostaglandins were becoming the circus mistress. The fact that Vane and his colleagues successfully demonstrated that the lungs were an important organ for the metabolism of endogenous mediators was an important concept which kept a stream of references to our early work. Unhappily, many other important papers are now 'unknown classics' perhaps because they had no luck to be made at the right time or, more importantly, at the right place, i.e., in a laboratory able to maintain a continuous rate of citation for a long period of time."

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