

This Week's Citation Classic®

Greaves M W, Søndergaard J & McDonald-Gibson W. Recovery of prostaglandins in human cutaneous inflammation. *Brit. Med. J.* 2:258-60, 1971.
[University Department of Dermatology, Newcastle upon Tyne, England]

We perfused skin inflamed by antigen challenge in volunteer patients with contact allergic dermatoses. Perfusates contained smooth-muscle-contracting activity that, upon further purification and analysis, turned out to be due to a mixture of E and F prostaglandins. This finding provided timely and much-needed direct evidence of the role of prostaglandins in human inflammation. [The *SCJ*⁹ indicates that this paper has been cited in over 205 publications.]

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Although Sam Shuster, who taught me clinical dermatology at Newcastle-upon-Tyne, was mainly responsible for stimulating my interest in inflammation and anti-inflammatory drugs, he and I wrote only one paper together, on the responses of human skin to putative mediators of inflammation.¹ It was obvious to us that any further progress in this field would depend on direct recovery of mediators from inflamed tissue, the accurate definition of these mediators, and the correlation of change in concentration with the intensity of the inflammatory reaction. What better milieu could there be for this purpose than inflamed human skin?

My PhD training in classical organ-bath pharmacology with H.O. Schild and J.L. Mongar at University College London showed me the value of perfused isolated guinea pig lung preparations in recovery and characterisation of mediators, and it occurred to Shuster and me that *in vivo* perfusion of skin of human volunteers was not beyond the realm of possibility.

The technique we used now seems unbelievably crude. Two wide-bore needles with holes perforated down the sides of the shaft were inserted into inflamed skin immediately subdermally in parallel, pointing in opposite directions along the long axis

of the flexor surface of the forearm. One needle was used to infuse an aqueous buffered isotonic saline solution, and the other was used to recover it. The assumption was that the perfused skin would behave as a sump for mediators released into the inflamed skin. That the method worked is more a tribute to the stoicism of our Newcastle Geordie volunteer patients than to the skills of the investigators!

I was joined by two able colleagues, Jørgen Søndergaard, a young investigative dermatologist from Gustav Asboe-Hansen's department in Copenhagen, and Wendy McDonald-Gibson, a graduate pharmacologist who had recently returned from the US. At about this same time (1970) John R. Vane published in *Nature* his results implicating inhibition of biosynthesis of prostaglandins in the mode of action of nonsteroid anti-inflammatory drugs.² McDonald-Gibson had been working in the US with Peter Ramwell and Jane Shaw on release of prostaglandins from frog skin. The pharmacological properties of the E prostaglandins and their ubiquitous distribution prompted Søndergaard and me to explore their release in human inflamed skin. We were greatly encouraged to find increased prostaglandin activity in sunburned erythematous skin due to UV-B irradiation (290-320 nm).

Subsequent studies carried out with Anne Kobza Black using a more refined blister-exudate suction-recovery method showed that both increased prostaglandin activity and the intensity of UV-B inflammation could be diminished by prior treatment with indomethacin,³ just as Vane had originally predicted.

Our work was important because it provided support in humans *in vivo* for the role of prostaglandins, which were relevant not only to inflamed skin but to other organs and tissues. Previous studies had relied almost exclusively on animal models. Furthermore, the perfusion method—rough and ready though it was—confirmed the value of this direct approach and prompted us to develop more sophisticated techniques that we have now applied to the recovery of other cyclooxygenase products and, more recently, lipoxigenase products in psoriasis, dermatitis, and other dermatoses.

Our recent studies in psoriasis, primary-irritant dermatitis, and urticaria^{4,5} have supported our view that eicosanoids play a part in the pathogenesis of these dermatoses. However, with the possible exception of ultraviolet inflammation, our data indicate a major role for leukotrienes and other lipoxigenase products rather than for the prostaglandins.

The research outlined was not particularly innovative despite its wide citation in the literature. It was important because it helped to establish the classical Dale criteria for implication of a mediator in a pathophysiological process and, especially, because the data derived from it were directly relevant to human disease.

1. Greaves M W & Shuster S. Responses of skin blood vessels to bradykinin, histamine and 5-hydroxytryptamine. *J. Physiology* 193:255-67, 1967.
2. Vane J R. Inhibition of prostaglandin synthesis as a mechanism of action of aspirin-like drugs. *Nature New Biol.* 231:232-5, 1971. (Cited 3,540 times.) [See also: Vane J R. Citation Classic. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 2: the molecules of life.* Philadelphia: ISI Press, 1986. p. 51.]
3. Greaves M W. Role of prostaglandins in inflammatory and proliferative skin disease. *J. Dermatology* 7:301-8, 1980.
4. ———. Prostaglandins and dermatology, the Ingram Lecture. *J. Roy. Coll. Phys. Lond.* 16:219-25, 1982.
5. Camp R D R & Greaves M W. Inflammatory mediators in the skin. *Brit. Med. Bull.* 43:401-14, 1987.