

Cockcroft D W, Ruffin R E, Dolovich J & Hargreave F E. Allergen-induced increase in non-allergic bronchial reactivity. *Clin. Allergy* 7:503-13, 1977.
[Regional Chest and Allergy Unit, Department of Medicine, St. Joseph's Hospital; and McMaster University, Hamilton, Ontario, Canada]

We documented an increase in airway responsiveness to histamine and methacholine in 7 of 13 subjects between seven hours and several days after single allergen inhalation tests. This appeared to occur in those subjects who had both an early and a late asthmatic response to allergen and not in those with an isolated early response. [The SCI® indicates that this paper has been cited in more than 590 publications.]

The Secret of Allergen-Induced Asthma

D.W. Cockcroft | Division of
Respiratory Medicine
Royal University Hospital
Saskatoon, Saskatchewan S7N 0X0
Canada

It is a pleasure to prepare a *Citation Classic* commentary on this paper. This investigation was performed during the early months of 1977 by Dick Ruffin and myself when we were research fellows working with F.E. Hargreave. We spent many challenging Saturdays and Sundays performing allergen, methacholine, and histamine inhalation tests in several research subjects. We documented that the degree of (nonallergic) airway hyperresponsiveness to both histamine and methacholine, a useful objective measure of the severity of variable air-flow obstruction and therefore, to an extent, of severity of asthma, increased substantially in the majority of subjects after a single allergen inhalation test.

The enhanced airway responsiveness was seen between seven hours and several days after allergen challenge, persisted beyond measurable changes in baseline FEV₁, was associated with increased asthma symptoms, and appeared in this initial investigation to be associated with the late asthmatic response. The late Roger Altounyan had observed similar increases in histamine airway responsiveness during seasonal allergen exposure.¹ However, this was the first documentation in the laboratory under controlled conditions and the first link to the late asthmatic response.

This investigation thus provided an explanation for the way in which allergens induce asthma. Subsequent studies have demonstrated in animals² and man³⁴ that allergen-induced airway inflammation is responsible for both the late response and the increased airway responsiveness.

This key observation was one step towards the recognition of asthma as primarily an inflammatory disease.⁵ It also provided a valuable link between inhaled allergens and respiratory pathophysiology, thus bringing together the fields of allergy and respiratory, which for so long had been on opposite sides of a controversy surrounding the relevance of allergens in the pathogenesis of asthma. Allergen-induced airway hyperresponsiveness also provides a useful clinical model to investigate the anti-inflammatory effects of asthma therapies.⁶

1. Altounyan R E C. Changes in histamine and atropine responsiveness as a guide to diagnosis and evaluation of therapy in obstructive airways disease. (Pepys J & Franklands A W, eds.) *Disodium eromoglycate in allergic airways disease*. London: Butterworths, 1970. p. 47-53.
2. Murphy K R, Wilson M C, Irvin C G, Glezen L S, Marsh W R, Haslet! C, Henson P M & Larsen G L. The requirement for polymorphonuclear leukocytes in the late asthmatic response and heightened airways reactivity in an animal model. *Amer. Rev. Resp. Dis.* 134:62-8. 1986.
3. de Monchy J G R, Kauffman H F, Venpe P, Koeter G H, Jansen H M, Sleuter H J & de Vries K. Bronchoalveolar eosinophilia during allergen-induced late asthmatic reactions. *Amer. Rev. Resp. Dis.* 131:373-6, 1985. (Cited 505 times.)
4. Gibson P G, Wong B J O, Hepperle M J E, Kline P A, Girgis-Gabartlo A, Guyatt G, Dolovich J, Denburg J A, Ramsdale E H & Hargreave F E. A research method to induce and examine a mild exacerbation of asthma by withdrawal of inhaled corticosteroid. *Clin. Experiment. Allergy* 22:525-32. 1992.
5. Kaliner M. Hypotheses on the contribution of late-phase allergic responses to the understanding and treatment of allergic diseases. *J. Allerg. Clin. Immunol.* 73:311-5, 1984.
6. Cockerolt D W & Murdock K Y. Comparative effects of inhaled salbutamol, sodium eromoglycate and oclomethasone dipropionate on allergen-induced early asthmatic responses, late asthmatic responses and increased bronchial responsiveness to histamine. *J. Allerg. Clin. Immunol.* 79:734-40. 1987. (Cited 180 times.)

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