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This Week's Citation Classic®

Cockcroft D W, Killian D N, Mellon J J A & Hargreave F E. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin. Allergy* 7:235-43, 1977.
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This paper describes a convenient and easy method for measuring airway hyperresponsiveness to inhaled histamine or methacholine, a usual feature of current asthma. Also included are a number of observations and correlations regarding both the presence and magnitude of histamine airway hyperresponsiveness in selected subjects with asthma, rhinitis, and undiagnosed cough, and in normals. [The *SCI*® indicates that this paper has been cited in more than 695 publications, making it the most-cited article from the journal.]

A Measured Breath

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This research took place between 1975 and 1977, during my two-year Medical Research Council of Canada research fellowship in F.E. Hargreave's laboratory in Hamilton, Ontario. European investigators had recognized for years that airways of asthmatics were hyperresponsive to "nonspecific" or nonsensitizing stimuli, such as histamine or cholinergic agonists. In the mid-1970s, the concept of measuring airway responsiveness with histamine or methacholine inhalation tests, both in clinical and research settings, was relatively new in North America.

The method described in this paper was modified from a method used in The Netherlands for more than 15 years.[1] As the method became established, we recognized and standardized a number of important technical aspects.[2,3] A standardized laboratory protocol outlining all important technical standardization features is just now being published.[4]

The method was established by Hargreave and D.N. Killian, prior to my arrival. Thus, my involvement in the research included performing, tabulating, and analyzing the data from 307 well-kept, characterized subjects, including normals and those with rhinitis, chronic nonproductive undiagnosed cough, and asthma of varying degrees of severity.

In addition to the method description, we made several observations and correlations. Some had been noted in a preliminary way by others; these included relationships between airway hyperresponsiveness and asthma severity (assessed by the minimum medication requirements), between airway hyperresponsiveness and reduced airway caliber (of modest significance), and a fairly high prevalence of airway hyperresponsiveness in subjects with rhinitis (particularly those with some chest symptoms). New observations included the high prevalence of airway hyperresponsiveness in subjects with nondiagnostic cough, the absence of airway hyperresponsiveness in subjects with seasonal asthma when tested out of season, and a small but significant correlation between the degree of airway hyperresponsiveness and the degree of atopy. All of these observations have since been confirmed by more specific studies.

This paper has been cited frequently, I am sure, because of the wealth of early and original observations in the field of airway hyperresponsiveness and asthma. However, most of the cites are because of the method itself. This method of measuring histamine and methacholine airway responsiveness has become widely used, particularly in Canada and the UK. Personal opinions as to its popularity would include its simplicity (both for subjects and technicians), its relative lack of expense compared with some other methods, and, importantly, the fact that its standardization has been exceedingly well documented.

1. de Vries K, Goei J T, Booy-Noord H & Orie N G M. Changes during 24 hours in the lung function and histamine hyperreactivity of the bronchial tree in asthmatic and bronchitic patients. *Int. Arch. Allergy Appl. Immunol.* 20:93-101, 1962. (Cited 175 times.)
2. Ryan G, Dolovich M B, Obminski G, Cockcroft D W, Juniper E, Hargreave F E & Newhouse M T. Standardization of inhalation provocation tests: influence of nebulizer output, particle size and method of inhalation. *J. Allerg. Clin. Immunol.* 67:156-61, 1981. (Cited 105 times.)
3. Cockcroft D W & Berscheid B A. Standardization of inhalation provocation tests: dose vs concentration of histamine. *Chest* 82:572-5, 1982. (Cited 15 times.)
4. Juniper E F, Cockcroft D W & Hargreave F E. Histamine and methacholine inhalation tests: tidal breathing method—laboratory procedure and standardization. Astra Pharma, Inc. 1990.

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