

# Allergen-induced asthma

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It was only in the late 19th century that specific allergens, pollen, animal antigens and, later, house dust mite, were identified to cause upper and lower airway disease. Early allergen challenge studies, crudely monitored before measurement of forced expiratory volume in 1 s became widespread in the 1950s, focused on the immediate effects but noted in passing prolonged and/or recurrent asthma symptoms. The late asthmatic response, recurrent bronchoconstriction after spontaneous resolution of the early responses occurring 3 h to 8 h or more postchallenge, has been identified and well characterized over the past 50 years. The associated allergen-induced airway hyper-responsiveness (1977) and allergen-induced airway inflammation (1985) indicate that these late sequelae are important in the mechanism of allergen-induced asthma. Allergens are now recognized to be the most important cause of asthma. A standardized allergen inhalation challenge model has been developed and is proving to be a valuable research tool in the investigation of asthma pathophysiology and of potential new pharmacological agents for the treatment of asthma.

**Key Words:** Allergen; Asthma; Challenge

Inhalant allergen exposure in atopic individuals is now recognized to be the single most important cause of asthma. In the current article, the history of our understanding of allergen-induced asthma is reviewed. This includes a focus on the remarkable achievements of Dr Frederick E Hargreave – known as ‘Freddy’ to friends and colleagues – and his many successful fellows. The present article was presented as the Canadian Thoracic Society Honourary Lecture at CHEST 2013, held in Chicago, Illinois (USA).

## HISTORY

Atopic allergic disease, including allergic rhinitis and allergic asthma, have undoubtedly been present since prehistoric times. There are reports that the Roman imperial family, including Julius Caesar and, particularly, Augustus Caesar (deceased 14 AD, 2000 years ago this year) had illnesses consistent with atopic allergic upper and lower airway disease (1). Britannicus (41 AD to 55 AD), stepbrother of Nero, was reported to be clinically highly allergic to horses. It is likely that the first medical report referring to allergic disease was from Leonardo Botallo (who described the ductus arteriosus) in 1565 and reported on primarily upper airway symptoms on exposure to roses, so-called ‘rose catarrh’ (2). There were numerous subsequent reports of this condition, which was believed to be relatively uncommon. We now appreciate that upper and lower airway allergic symptoms associated with roses are almost certainly due to the invisible concomitant airborne pollen exposure, most likely grass pollen. The first good clinical description of allergic rhinitis and asthma is attributed to Jonathan Bostock less than 200 years ago (3). In 1819, he reported on his own affliction with rhinitis and asthma commencing annually in mid-June (grass pollen season). He termed the condition ‘summer catarrh’ and incorrectly attributed the cause to heat and humidity. The popular term ‘hay fever’ emerged in the middle of the 19th century as individuals described symptoms on exposure to new-mown hay (also likely an allergy to grasses). In 1872, Wyman (4) described autumnal catarrh

## L’asthme induit par des allergènes

On a découvert seulement à la fin du XIX<sup>e</sup> siècle que des allergènes précis, soit le pollen, des antigènes des animaux et, plus tard, les acariens, étaient responsables des maladies des voies respiratoires supérieures et inférieures. Les premières études sur les épreuves aux allergènes, surveillées grossièrement avant que la mesure du volume expiratoire maximal par seconde se généralise dans les années 1950, étaient axées sur les effets immédiats, mais observées en cas de symptômes d’asthme prolongé ou récurrent. Les réponses asthmatiques tardives, la bronchoconstriction récurrente après une résolution spontanée des réponses précoces se déclarant au moins trois à huit heures après les épreuves, sont démontrées et bien caractérisées depuis 50 ans. L’hyperréaction connexe des voies respiratoires induite par les allergènes (1977) et l’inflammation des voies respiratoires induite par les allergènes (1985) démontrent que ces séquelles tardives sont importantes dans le mécanisme de l’asthme induit par des allergènes. On sait désormais que les allergènes sont la principale cause de l’asthme. Une épreuve standardisée d’inhalation d’allergènes a été mise au point et se révèle un outil de recherche précieux dans l’examen de la physiopathologie de l’asthme et des nouveaux agents pharmacologiques potentiels pour le traiter.

and was able to induce both rhinitis and asthma in himself by sniffing ragweed. In 1882, Henry Hyde Salter (5) reported on asthma precipitated by exposure to cats and rabbits, and later on to horses and dogs. In 1873, Charles Blackley, in his monograph entitled *Catarrhus Æstivus* (6), identified grass pollen as the (or at least one) cause of rhinitis, conjunctivitis and asthma; all of his clinical experiments were performed on himself because he claimed he was unable to convince any other sufferers to participate in his trials. The idea that pollen contained a toxin was popular (7) and led to the development of pollen inoculation (allergen injection therapy), which proved to be effective despite the incorrect rationale (8). In 1921, passive transfer of sensitivity using the serum of a highly fish-allergic individual pointed to a serum factor as being a cause of the syndrome (9). The terms ‘reagin’ (or reaginic antibody) and ‘atopy’ were coined in 1923 (10). It was not until 1967 that immunoglobulin E (Ig E) was identified as the nature of the reaginic antibody (11).

## ALLERGEN CHALLENGE HISTORY

Clinical allergen challenges began with Charles Blackley (6). Throughout the first half of the 20th century, there were scattered reports of allergen challenge being performed to test the clinical relevance of various allergens. These reports all focused on the immediate response, the so-called ‘early asthmatic response’ (EAR), which develops shortly after exposure. Expiratory flow rates had not yet been introduced; the response to allergen was measured fairly crudely by such things as symptoms, heavy breathing and chest auscultation. When objective measurements of lung function were made, it was only the vital capacity that was measured and it was not uncommon to see reports of 35% to 50% reduction in vital capacity; this represents a very marked degree of bronchoconstriction. Tiffeneau (12) introduced forced expiratory volume in 1 s (FEV<sub>1</sub>) in 1947 and suggested that this would be a useful measurement to study the effect of drugs (bronchoconstrictors, bronchodilators) and allergens in asthma.

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The 'late asthmatic response' (LAR), which we now recognize as a recurrence of bronchoconstriction developing between 3 h and  $\geq 8$  h after allergen challenge and after spontaneous resolution of the EAR (13), was a term first coined in 1951 by Herxheimer (14). A review of previous challenge study reports shows that Blackley described a classic late asthmatic response due to his own overdose of grass pollen, and that many of the early allergen challenge reports noted that recurrent or prolonged symptoms were sometimes induced. Herxheimer himself was still monitoring his challenges with vital capacity up to 50% decline, and suspected that many of the late responses were actually a continuous response with interval transient improvement after isoproterenol had been administered to treat the early response (14). Ten years later, there was an excellent description of mite-induced dual asthmatic responses (DAR) (15). In the late 1960s and early 1970s, Jack Pepys (16,17) and Dick Orié (18,19), working independently in the United Kingdom and the Netherlands, respectively, characterized the DAR to inhaled allergens. There was an ongoing controversy as to whether the late response was caused by IgG precipitins (Pepys) or not (Orié). The 'pro' argument related to the timing of the response similar to that seen in extrinsic allergic alveolitis (EAA), and the fact that many of Pepys' subjects were challenged with *Aspergillus* to which precipitins were present (20). The 'con' argument, related to observations that the LAR was obstructive (not restrictive), was not associated with systemic symptoms such as seen in EAA, and that precipitins were not present to the common aeroallergens house dust mite, pollen or animal danders (21). The IgE dependence of late responses was shown by Jerry Dolovich and Freddy Hargreave in the skin in 1973 (22), and confirmed in the airway in 1986 (23) (both studies using polyclonal anti-human IgE) and for the residual skeptics in 1997 when LARs were shown to be inhibited exceptionally well by the monoclonal anti-IgE omalizumab (24). The first classical graphic description of a DAR with an uninterrupted time axis appears to be from Freddy Hargreave's ragweed challenge asthma article in 1974 (25).

#### ALLERGEN-INDUCED INCREASE IN AIRWAY RESPONSIVENESS

Measurement of airway hyper-responsiveness (AHR) was pioneered by Tiffeneau in the 1940s (26) and had become quite popular in the 1960s in Europe. Challenge protocols were published in North America in the late 1970s (27). AHR was regarded as a classic feature of asthma. There was no appreciation of the possibility that AHR had the potential to vary over time to any degree and with any speed. Roger Altounyan, whose first two claims to fame were the synthesis of sodium cromoglycate and nedocromil (28), and as a role model along with his siblings for the Swallows in Arthur Ransome's iconic adolescent series *Swallows and Amazons* (29) did recognize seasonal AHR. His findings are buried in his 1964 article, in which he made the observation that AHR to histamine was stable except in grass pollen asthmatics who demonstrated marked seasonal increases in AHR (30). It was Dick Ruffin and I, working in Freddy Hargreave's laboratory who, in 1977, documented increased airway responsiveness to both histamine and methacholine 7 h and 30 h following allergen challenges (31). The changes were sometimes marked (up to 10-fold) and lasted for up to seven to 10 days, and appeared to be associated with allergen-induced LARs. Follow-up studies in Freddy's laboratory documented a definite correlation of allergen-induced AHR, both in magnitude and duration (32), with the LAR and also documented that individuals demonstrating this in the laboratory were those who were more likely to develop seasonal AHR during ragweed pollen season (33). This previously unrecognized (and somewhat unexpected) observation marked an important change in our thinking about allergen-induced asthma.

#### ALLERGEN-INDUCED AIRWAY INFLAMMATION

Early investigators had speculated that the LAR was likely associated with more than just bronchoconstriction and postulated the existence or coexistence of inflammation. De Monchy's classic bronchoscopy

study in 1985 documented marked airway eosinophilia 7 h after allergen challenge in individuals with a DAR (34). This was not seen 7 h after allergen challenge in normal individuals or nonresponding asthmatics. Relatively minor airway eosinophilia was seen 7 h after allergen challenge in subjects with an isolated EAR and 3 h after allergen challenge in subjects with a DAR. While investigations were generally performed in different individuals (n=5 per group), there were two subjects who participated in the 3 h and 7 h DAR bronchoscopies. Longitudinal studies pre- and post-allergen in Freddy Hargreave's laboratory using induced sputum analysis documented significant increases in airway eosinophils and airway metachromatic cells (mast cells, basophils) after allergen challenge (35).

Collectively, the late sequelae following allergen challenge including the LAR, increased AHR and increased airway inflammation, appeared to be linked to one another and, unlike the allergen-induced EAR, are mimickers of clinical asthma. Over this time period, our ideas have changed. Allergens were once recognized as one of many causes of bronchoconstriction in asthmatics, whereas they are now recognized as an important and major cause (the most common cause) of asthma. It has been attractive to speculate that airway inflammation is the cause of late sequelae; however, investigations with an anti-interleukin 5 monoclonal antibody appeared to divorce the late response and increased responsiveness from at least eosinophilic inflammation (36). The non-cellular aspect of inflammation may be important; however, the precise mechanism(s) of these late sequelae remain incompletely understood.

#### THE ALLERGEN CHALLENGE MODEL

Allergen challenge is a research tool exclusively for the study of asthma pathophysiology and for investigation of novel treatments. The standardized method involves capturing the EAR, the LAR, and the changes in both AHR and inflammation (37). The pharmacology with current asthma drugs is as follows. Inhaled beta-agonists inhibit the EAR but not the LAR (38), inhaled corticosteroids (ICS) inhibit the LAR but not the EAR (38), while cromones (16,19,38) and leukotriene receptor antagonists (LTRAs) (39) inhibit both. ICS given 2 h after the challenge will inhibit the LAR (40). Phosphodiesterase inhibitors (41-43) and inhaled anticholinergic bronchodilators (44) have minimal effects. Regular use of beta-agonists enhance all aspects of the allergen response (45,46).

We hypothesize that the allergen challenge model primarily examining the late sequelae should be a valuable tool for investigation of new, potentially effective asthma therapies. This is based on allergen challenge responses to known effective drugs (particularly ICS, LTRAs and cromones), the minimal effectiveness of phosphodiesterase inhibitors and the lack of effectiveness of beta<sub>2</sub>-agonists and anticholinergics. A clinically ineffective ICS was shown to be ineffective in the allergen challenge model when comparing a known effective ICS (47).

#### ALLERGEN NCE CLINICAL INVESTIGATIVE COLLABORATIVE

Several of Freddy's former fellows have previously performed multicentre allergen challenge studies (46-48). The Allergy, Genes and Environment National Centres of Excellence (AllerGen NCE) Clinical Investigative Collaborative (CIC) is cochaired by Drs Paul O'Byrne and Louis-Philippe Boulet; I was a founding member. We have recently added investigators in Calgary and Edmonton (Alberta), Vancouver (British Columbia) and Stockholm (Sweden). This is a multicentre clinical collaboration performing industry-sponsored studies with exciting new molecules mainly using the allergen challenge model. Over the first seven years (2006 to 2013), we have performed 16 DAR studies, two using only the EAR and one methacholine study. This has resulted in numerous publications (49-53) and presentations. Many of the molecules have demonstrated significant and promising effects. The most effective molecules we have studied to this point would be an ultra-long-acting beta-agonist effect on the magnitude

and duration of protection against methacholine-induced bronchoconstriction (51), and the ability of IgE molecules to inhibit the EAR. To date, the best LAR inhibitor we have seen is an anti-interleukin 13 molecule (52). The group continues to collaborate on the investigation of new and exciting molecules.

### SUMMARY

Our understanding of causes and mechanisms of allergen-induced asthma has increased exponentially over the past few decades. It is now appreciated that allergen exposure in sensitized individuals is a genuine cause of asthma and is probably the most common etiological

factor in the disease we know as asthma. A standardized allergen challenge model addressing the late sequelae (LAR, induced AHR and induced inflammation) has proven valuable in investigating asthma pathogenesis, pathophysiology and pharmacology. Much of this increased understanding can be attributed to the pioneering work of Freddy Hargreave, his colleague Jerry Dolovich and Freddy's numerous former fellows.

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### REFERENCES

- Cantini A. Asthma. In: Pediatric Allergy, Asthma and Immunology. Heidelberg: Springer-Verlag, 2008:725.
- Simons FER. Ancestors of Allergy. New York: Global Medical Communications Ltd, 1994:78-9.
- Bostock J. Case of a periodical affection of the eyes and chest. *Medico Chirurgical Transactions* 1819;10:161-4.
- Wyman M. Autumnal Catarrah. Cambridge: Hurd and Houstin, 1872.
- Salter HH. Asthma: Its Pathology and Treatment, 3rd edn. New York: William Wood & Co, 1982.
- Blackley CH. Experimental Researches on the Causes and Nature of Catarrhus Æstivus. London: Ballière Tindall & Cox, 1873.
- Dunbar WP. The present state of our knowledge of hay fever. *J Hygiene* 1913;13:105-48.
- Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911;1:1572.
- Prausnitz C, Kustner H. Studien uber Ueberempfindlichkeit. *Centralb Bakteriol I Abt Orig* 1921;86:160. Translated by Prausnitz C. In: Gell PGH, Coombs RRA, eds. *Clinical Aspects of Immunology*. Oxford: Blackwell Scientific Publications, 1962:808-16.
- Coca AF, Cooke RA. On the classification of the phenomena of hypersensitiveness. *J Immunol* 1923;8:163-82.
- Ishizaka K, Ishizaka T. Identification of gamma-E-antibodies as a carrier of reaginic activity. *J Immunol* 1967;99:1187-98.
- Tiffeneau R, Pinelli A. Air circulant et air captif dans l'exploration de la fonction ventilatrice pulmonaire. *Paris Méd* 1947;37:624-8.
- O'Byrne PM, Dolovich J, Hargreave FE. State of the art: Late asthmatic responses. *Am Rev Respir Dis* 1987;136:740-51.
- Herxheimer H. The late bronchial reaction in induced asthma. *Int Arch Allergy Appl Immunol* 1952;3:323-33.
- Burtin P, Buffe D, Carton J, Dominjon-Monnier F, Kourilsky R. L'allergie retardée à la poussière de maison. *Int Arch Allergy* 1962;21:8-19.
- Pepys J, Chan M, Hargreave FE, McCarthy DS. Inhibitory effects of disodium cromoglycate on allergen-inhalation tests. *Lancet* 1968;2:134-7.
- Pepys J, Davies RJ, Breslin ABX, Hendricks DJ, Hutchcroft BJ. The effects of inhaled beclomethasone dipropionate (Becotide) and sodium cromoglycate on asthmatic reactions to provocation tests. *Clin Allergy* 1974;4:13-24.
- Van Lookeren Campagne JG, Knol K, deVries K. House dust provocation in children. *Scand J Respir Dis* 1969;50:76-85.
- Booij-Noord H, Orié NGM, deVries K. Immediate and late bronchial obstructive reactions to inhalation of house dust and protective effects of disodium cromoglycate and prednisolone. *J Allergy Clin Immunol* 1971;48:344-54.
- Pepys J. Immunological mechanisms in asthma. In: Porter R, Birch J, eds. *Identification of Asthma*. London: Churchill Livingstone, 1971:87-97.
- Orié NGM, Van Lookeren Campagne JG, Knol K, Booij-Noord H, deVries K. Late reactions in bronchial asthma. In: Pepys J, Yamamura I, eds. *Intal in Bronchial Asthma*. Tokyo: Proceedings of the 8th International Congress of Allergology, 1974:17-29.
- Dolovich J, Hargreave FE, Chalmers R, Shier KJ, Gaudie J, Bienenstock J. Late cutaneous allergic responses in isolated IgE-dependent reactions. *J Allergy Clin Immunol* 1973;52:38-46.
- Kirby JG, Robertson DG, Hargreave FE, Dolovich J. Asthmatic responses to inhalation of anti-human IgE. *Clin Allergy* 1986;16:191-4.
- Fahy JV, Fleming HE, Wong HH, et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med* 1997;155:1828-34.
- Robertson DG, Kerigan AT, Hargreave FE, Chalmers R, Dolovich J. Late asthmatic responses induced by ragweed pollen allergen. *J Allergy Clin Immunol* 1974;54:244-54.
- Tiffeneau R, Beauvallet M. Epreuve de bronchoconstriction et de bronchodilatation par aerosols. *Bull Acad de Med* 1945;129:165-8.
- Cockcroft DW, Killian DN, Mellon JJA, Hargreave FE. Bronchial reactivity to inhaled histamine: A method and clinical survey. *Clin Allergy* 1977;7:235-43.
- Orr TSC, Roger Altounyan: The man and his work. *Respir Med* 1989;83(Suppl):3-6.
- Ransome A. Swallows and Amazons. London: Jonathan Cape, 1930.
- Altounyan REC. Variation of drug action on airway obstruction in man. *Thorax* 1964;19:406-15.
- Cockcroft DW, Ruffin RE, Dolovich J, Hargreave FE. Allergen-induced increase in nonallergic bronchial reactivity. *Clin Allergy* 1977;7:503-13.
- Cartier A, Thomson NC, Frith PA, Roberts R, Hargreave FE. Allergen-induced increase in bronchial responsiveness to histamine: Relationship to the late asthmatic response and change in airway caliber. *J Allergy Clin Immunol* 1982;70:170-7.
- Boulet L-P, Cartier A, Thomson NC, Roberts RS, Dolovich J, Hargreave FE. Asthma and increases in nonallergic bronchial responsiveness from seasonal pollen exposure. *J Allergy Clin Immunol* 1983;71:399-406.
- de Monchy JGR, Kauffman HF, Venge P, et al. Bronchoalveolar eosinophilia during allergen-induced late asthmatic reactions. *Am Rev Respir Dis* 1985;131:373-6.
- Pin I, Freitag AP, O'Byrne PM, et al. Changes in the cellular profile of induced sputum after allergen-induced asthmatic responses. *Am Rev Respir Dis* 1992;145:1265-9.
- Leckie MJ, ten Brinke A, Khan J, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyperresponsiveness, and the late asthmatic response. *Lancet* 2000;356:2144-8.
- Boulet LP, Gauvreau G, Boulay ME, O'Byrne P, Cockcroft DW; Clinical Investigative Collaboration, Canadian Network of Centers of Excellence AllerGen. The allergen bronchoprovocation model: An important tool for the investigation of new asthma anti-inflammatory therapies. *Allergy* 2007;62:1101-10.
- Cockcroft DW, Murdock KY. Comparative effects of inhaled salbutamol, sodium cromoglycate and beclomethasone dipropionate on allergen-induced early asthmatic responses, late asthmatic responses and increased bronchial responsiveness to histamine. *J Allergy Clin Immunol* 1987;79:734-40.
- Davis BE, Illamperuma C, Gauvreau GM, et al. Single-dose desloratadine and montelukast and allergen-induced late airway responses. *Eur Respir J* 2009;33:1302-8.
- Cockcroft DW, McParland CP, O'Byrne PM, et al. Beclomethasone given after the early asthmatic response inhibits the late response and the increased methacholine responsiveness and cromolyn does not. *J Allergy Clin Immunol* 1993;91:1163-8.
- Pauwels R, van Renterghem D, Van Der Straeten M, Johannesson N, Persson GA. The effect of theophylline and enprofylline on allergen-induced bronchoconstriction. *J Allergy Clin Immunol* 1985;76:583-90.

42. Cockcroft DW, Murdock KY, Gore BP, O'Byrne PM, Manning P. Theophylline does not inhibit allergen-induced increase in airway responsiveness to methacholine. *J Allergy Clin Immunol* 1988;83:913-20.
  43. Gauvreau GM, Boulet LP, Schmid-Wirlitsch C, et al. Roflumilast attenuates allergen-induced inflammation in mild asthmatic subjects. *Respir Res* 2011;12:140.
  44. Cockcroft DW, Ruffin RE, Hargreave FE. Effect of Sch 1000 in allergen-induced asthma. *Clin Allergy* 1978;8:361-72.
  45. Cockcroft DW, McParland CP, Britto SA, Swystun VA, Rutherford BC. Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1993;342:833-7.
  46. Gauvreau GM, Watson RM, Jordana M, Cockcroft D, O'Byrne PM. The effect of regular inhaled salbutamol on allergen-induced airway responses and inflammatory cells in blood and induced sputum. *Am J Respir Crit Care Med* 1995;151:A39.
  47. Kidney JC, Boulet LP, Hargreave FE, et al. Evaluation of single-dose inhaled corticosteroid activity with an allergen challenge model. *J Allergy Clin Immunol* 1997;100:65-70.
  48. Gauvreau GM, Becker AB, Boulet LP, et al. The effects of an anti-CD11a mAb, efalizumab, on allergen-induced airway responses and airway inflammation in subjects with atopic asthma. *J Allergy Clin Immunol* 2003;112:331-8.
  49. Gauvreau GM, Boulet LP, Cockcroft DW, et al. Antisense therapy against CCR3 and the common beta chain attenuates allergen-induced eosinophilic responses. *Am J Respir Crit Care Med* 2008;177:952-8.
  50. Duong M, Cockcroft D, Boulet LP, et al. The effect of IVX-0142, a heparin-derived hypersulfated disaccharide, on the allergic airway responses in asthma. *Allergy* 2008;63:1195-201.
  51. O'Byrne PM, van der Linde J, Cockcroft DW, et al. Prolonged bronchoprotection against inhaled methacholine by inhaled BI 1744, a long-acting beta(2)-agonist, in patients with mild asthma. *J Allergy Clin Immunol* 2009;124:1217-21.
  52. Gauvreau GM, Boulet LP, Cockcroft DW, et al. Effects of interleukin-13 blockade on allergen-induced airway responses in mild atopic asthma. *Am J Respir Crit Care Med* 2011;183:1007-14.
  53. Gauvreau GM, Boulet LP, Cockcroft DW, et al. OX40L blockade and allergen-induced airway responses in subjects with mild asthma. *Clin Exp Allergy* 2014;44:29-37.
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