REFERENCES

1. Kelly MM, Leigh R, Jayaram L, Goldsmith CH, Parameswaran K, Hargreave FE. Eosinophilic bronchitis in asthma: a model for establishing dose-response and relative potency of inhaled corticosteroids. J Allergy Clin Immunol 2006;117:989-94.
2. Gibson PG, Fujimura M, Niimi A. Eosinophilic bronchitis: clinical manifestations and implications for treatment. Thorax 2002;57:178-82.
3. Thomson NC, Chaudhuri R. Why is eosinophilic bronchitis not asthma? Am J Respir Crit Care Med 2004;170:4-5.
4. Kanazawa H, Nomura S, Yoshikawa J. Role of microvascular permeability on physiologic differences in asthma and eosinophilic bronchitis. Am J Respir Crit Care Med 2004;169:1125-30.
5. Brightling CE, Symon FA, Birring SS, Bradding P, Wardlaw AJ, Pavord ID. Comparison of airway immunopathology of eosinophilic bronchitis and asthma. Thorax 2003;58:528-32.
6. Brightling CE, Bradding P, Symon FA, Holgate ST, Wardlaw AJ, Pavord ID. Mast-cell infiltration of airway smooth muscle in asthma. N Engl J Med 2002;346:1699-705.
7. Berry MA, Hargadon B, McKenna S, Shaw D, Green RH, Brightling CE, et al. Observational study of the natural history of eosinophilic bronchitis. Clin Exp Allergy 2005;35:598-601.

Available online September 12, 2006.
doi:10.1016/j.jaci.2006.06.045

Reply

To the Editor:

We thank Drs Agarwal and Gupta[1] for their correspondence regarding our article entitled ''Eosinophilic bronchitis in asthma: a model for establishing dose-response and relative potency of inhaled corticosteroids.''[2] The issue they raise is one of semantics. By suggesting that our use of the term *eosinophilic bronchitis in asthma* might be confusing to the reader, they demonstrate the adoption of an essentialist rather than a nominalist philosophy. Essentialists use words in an abstract fashion to imply that diseases be classified in a logical sequence of mutually exclusive categories and talk of diseases as if they exist as real entities. In this case the *words* eosinophilic bronchitis are displaced by the *concept* of eosinophilic bronchitis as a disease. We believe that essentialist definitions have no place in science.

We prefer to use a nominalist approach in science, in which words are used to mean what they say and not refer to abstract concepts. The original description of eosinophilic bronchitis without asthma came from our group in Hamilton,[3] and we continue to hold the view that *eosinophilic bronchitis* is a nominal term used to describe an eosinophilic cellular infiltrate of the bronchial wall. As such, the term is not specific to any single disease entity and can occur in asthma (most commonly),[4,5] occupational lung disease,[6] smoking-related chronic obstructive pulmonary disease,[7,8] or a number of other airway inflammatory conditions.

Induced sputum analysis measures inflammatory cells within the airway lumen. To get to the lumen, cells need to transgress through the airway wall, and the presence of sputum eosinophilia is therefore an appropriate measurement to detect the presence of eosinophilic bronchitis.[9] Drs Agarwal and Gupta apparently failed to appreciate that the original publication from our group,[3] as well as subsequent publications[10,11] on the entity of eosinophilic bronchitis in patients with chronic cough, normal spirometric results, and airway responsiveness used the term *eosinophilic bronchitis without asthma* to characterize these patients.

The use of the term *eosinophilic bronchitis in asthma* in our recent study is justified on the basis that asthma is characterized by the presence of variable airflow limitation, airway hyperresponsiveness, and eosinophilic airway inflammation. In this study the primary outcome was a decrease in sputum eosinophil counts as a surrogate marker of eosinophilic bronchitis. Changes in spirometric results, airway hyperresponsiveness, exhaled nitric oxide levels, or patient symptom scores, although all valid alternative outcomes in asthma trials, were not the primary outcome in this study. We therefore believe that the title of our article, ''Eosinophilic bronchitis in asthma: A model for establishing dose-response and relative potency of inhaled corticosteroids,'' is nominally accurate, clinically appropriate, and devoid of any confusion to the reader.

Margaret M. Kelly, MBChB[a,c]
Richard Leigh, MBChB, PhD[a]
Lata Jayaram, MBChB[a]
Charlie H. Goldsmith, PhD[b]
Krishnan Parameswaran, MD, PhD[a]
Frederick E. Hargreave, MD[a]

From the [a]Airways Research Group, Firestone Institute for Respiratory Health, and [b]Department of Clinical Epidemiology and Biostatistics, Centre for Evaluation of Medicines, St Joseph's Healthcare–McMaster University, Hamilton, Ontario, Canada [c]Immunology Research Group, Institute of Infection, Immunity and Inflammation, University of Calgary, Calgary, Alberta, Canada.

Disclosure of potential conflict of interest: R. Leigh has consultant arrangements with GlaxoSmithKline Canada Inc and AstraZeneca Canada Inc and has received honoraria from AstraZeneca Canada Inc, Boehringer Ingelheim Canada Inc, and Pfizer Canada Inc. K. Parameswaran has received grant support from GlaxoSmithKline and Sepracor. The rest of the authors have declared that they have no conflict of interest.

REFERENCES

1. Agarwal R, Gupta D. Eosinophilic bronchitis and asthma with sputum eosinophilia are different entities. J Allergy Clin Immunol 2006;118:969-70.
2. Kelly MM, Leigh R, Jayaram L, Goldsmith CH, Parameswaran K, Hargreave FE. Eosinophilic bronchitis in asthma: a model for establishing dose-response and relative potency of inhaled corticosteroids. J Allergy Clin Immunol 2006;117:989-94.
3. Gibson PG, Dolovich J, Denburg JA, Ramsdale EH, Hargreave FE. Chronic cough: eosinophilic bronchitis without asthma. Lancet 1989;1:1346-8.
4. Gibson P, Girgis-Gabardo A, Morris MM, Mattoli S, Kay JM, Dolovich J, et al. Cellular characteristics of sputum from patients with asthma and chronic bronchitis. Thorax 1989;44:693-9.
5. Pizzichini MMM, Popov T, Efthimiadis A, Hussack P, Evans S, Pizzichini E, et al. Spontaneous and induced sputum to measure indices of airway inflammation in asthma. Am J Respir Crit Care Med 1996;154:866-9.
6. Lemiere C, Chaboilliez S, Trudeau C, Taha R, Maghni K, Martin JG, et al. Characterization of airway inflammation after repeated exposures to occupational agents. J Allergy Clin Immunol 2000;106:1163-70.
7. Hargreave FE, Leigh R. Induced sputum, eosinophilic bronchitis, and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;160(suppl):S53-7.
8. Leigh R, Pizzichini MM, Morris MM, Maltais F, Hargreave FE, Pizzichini E. Stable COPD: predicting benefit from high-dose inhaled corticosteroid treatment. Eur Respir J 2006;27:964-71.

9. Pavord ID, Sterk PJ, Hargreave FE, Kips JC, Inman MD, Louis R, et al. Clinical applications of assessment of airway inflammation using induced sputum. Eur Respir J Suppl 2002;37:40s-3s.
10. Brightling CE, Ward R, Goh KL, Wardlaw AJ, Pavord ID. Eosinophilic bronchitis is an important cause of chronic cough. Am J Respir Crit Care Med 1999;160:406-10.
11. Hancox RJ, Leigh R, Kelly MM, Hargreave FE. Eosinophilic bronchitis [letter]. Lancet 2001;358:1104.

Available online September 12, 2006.
doi:10.1016/j.jaci.2006.06.044

The metal binding site of the major house dust mite allergen Der p 1

To the Editor:

In their recent article, de Halleux et al[1] reported the crystal structure of mature Der p 1. We have previously published an article describing the structure of the same allergen containing the propeptide.[2] Our article is correctly acknowledged and referenced in the de Halleux article. However, unfortunately, the authors claim to have discovered a metal binding site that they state has not been described in our article: ''Recently, the 3-dimensional structure of the pro-form of Der p 1 has been presented by Meno et al. Careful examination of their data shows that a metal binding site is also present in pro–Der p 1, though it is not mentioned in their article.'' This metal site is clearly described in our article:

> Strong F_o-F_c electron density was observed in a depression on the surface of rproDer p 1-CN. A Y^{3+} ion complex-bound to the side chain carboxylic acid groups of D136, E139, and E171, the backbone carbonyl oxygen of L137, and three water molecules was placed at this position, and it returned nice electron density with a final B-factor of 16.7 $Å^2$. Two of the complex-bound water molecules hydrogen bond to a symmetry-related rproDer p 1-CN molecule through a hydrogen bonding network involving several other water molecules and a well ordered sulfate ion. This could explain the major improvement in crystal quality observed when YCl_3 was included in the crystallization.[2]

The amino acid residues that coordinate the yttrium ion are the same as those that coordinate the magnesium ion in the de Halleux article (the 80-residue discrepancy in the residue numbering is due to the presence of the propeptide). We find this misrepresentation most unfortunate because it is a substantial finding and because we believe that the statement in the de Halleux article suggests that they have examined our data and located a metal ion that we overlooked. This is certainly not the case because it is described both in our article, as well as in the corresponding Protein Data Bank entry (1XKG). Having said this, the biologic significance of the metal-binding site remains obscure. Enzyme kinetic measurements on Der p 1 are usually performed in the presence of EDTA to prevent cation-facilitated inactivation of the active site cysteine residue, and therefore the metal binding site is unlikely to be occupied under these conditions. Omitting the EDTA and adding magnesium or calcium ions increases the enzymatic activity of the homologous protease papain somewhat,[3] but this enzyme does not harbor the metal-binding site in question. It is tempting to speculate that the metal ion plays a role in stabilizing the Der p 1 structure, as suggested in the de Halleux article. However, magnesium or calcium ions have been shown to decrease the thermal stability of papain,[3] and therefore the effect of metal ions remains to be investigated further for Der p 1. The observation that both yttrium and magnesium ions can bind at this site despite their different ionic radii suggests that the metal binding site is flexible.

Kåre Meno, PhD[a]
Peter B. Thorsted, PhD[a]
Henrik Ipsen, MSc[a]
Ole Kristensen, PhD[b]
Jørgen N. Larsen, PhD[a]
Michael D. Spangfort, PhD[a]
Michael Gajhede, PhD[b]
Kaare Lund, PhD[a]

From [a]the Research Department, ALK-Abelló A/S, Hørsholm, Denmark, and [b]the Department of Medicinal Chemistry, Danish University of Pharmaceutical Sciences, Copenhagen, Denmark.

Disclosure of conflict of interest: K. Meno, P. B. Thorsted, H. Ipsen, J. N. Larsen, M. D. Spangfort, and K. Lund are all employed by ALK-Abelló. The rest of the authors have declared that they have no conflict of interest.

Editor's note: *de Halleux et al[1] have acknowledged their omission in not citing the work of Meno et al[2] and extend their sincere apology to the authors.*

REFERENCES

1. de Halleux S, Stura E, VanderElst L, Carlier V, Jacquemin M, Saint-Remy JM. Three-dimensional structure and IgE-binding properties of mature fully active Der p 1, a clinically relevant major allergen. J Allergy Clin Immunol 2006;117:571-6.
2. Meno K, Thorsted PB, Ipsen H, Kristensen O, Larsen JN, Spangfort MD, et al. The crystal structure of recombinant proDer p 1, a major house dust mite proteolytic allergen. J Immunol 2005;175:3835-45.
3. Kaul P, Sathish HA, Prakash V. Effect of metal ions on structure and activity of papain from Carica papaya. Nahrung 2002;46:2-6.

Available online August 29, 2006.
doi:10.1016/j.jaci.2006.06.038