

Lastly, I would like to acknowledge the company for which Drs McDermott and O'Dowd work, AstraZeneca. They have provided support for many of the long-term studies on growth that have advanced our knowledge, and the scientific and clinical communities are indebted to them.

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The “giant faces” of nitric oxide in asthma: Role for the inducible and the constitutive nitric oxide synthase isoforms

To the Editor:

Evaluating a group of asthmatic children and adolescents taking no asthma controller medications, the Childhood Asthma Research and Education Network observed that fractional exhaled nitric oxide (FENO) levels positively correlated with inflammatory markers and with the degree of allergen sensitization but were only weakly related to airway obstruction (FEV₁/forced vital capacity), bronchodilator reversibility, and methacholine responsiveness.¹

These data, which are consistent with those of previous studies in adults and children,^{2–5} raise a question: Why, in asthmatic patients, is it easier to demonstrate a link between FENO levels and airway or systemic inflammation than between FENO levels and airflow limitation, bronchial hyperresponsiveness, or both? The answer might come from the hypothetical different activities of the different concentrations of nitric oxide (NO) generated by the 2 NO synthase isoforms: the inducible nitric oxide synthase (iNOS) and the constitutive nitric oxide synthase (cNOS) isoforms.⁶ The expression of iNOS is induced by proinflammatory cytokines and results in a protracted and Ca²⁺-independent release of high levels of NO (in the nanomolar range)⁷ by structural and inflammatory cells within the airways, which is associated with proinflammatory effects.⁶

In contrast with iNOS, cNOS releases small amounts of NO (in the picomolar range) after agonist-receptor activation within seconds in response to increases in cytosolic Ca²⁺, and it appears to be involved in the protection against bronchoconstriction induced by agonists, such as bradykinin and adenosine monophosphate.⁶ In vitro studies showed that bronchoprotective Ca²⁺-dependent NO derives from airway epithelium.⁶ Human in vivo studies confirmed that in moderate-to-severe asthma, the release of bronchoprotective NO is impaired,⁶ probably because of epithelial dysfunction or damage caused by an exaggerated inflammatory environment. In line with the latter, a more recent study demonstrated that in atopic patients with mild asthma, allergen-induced increase in airway hyperresponsiveness to bradykinin is dependent on deficient release of protective NO in relation to a down-regulated expression of endothelial cNOS in airway epithelium.⁸

All of these data support the hypothesis that cNOS might be involved in the regulation of bronchomotor tone in asthma, and probably the congenital (eg, polymorphism) or acquired (eg, inflammatory process) impaired activation of the constitutive enzymatic isoform of NOS might potentiate airway hyperresponsiveness and subsequently influence the appearance of the clinical symptoms.

On the basis of this hypothesis, although the high levels of iNOS-derived NO should be considered an important biomarker of inflammatory activity in asthma, opposing effects (“giant faces”) could be played by the low levels of cNOS-derived NO (ie, having a protective role in asthma). Further in vitro and in vivo studies are warranted to definitively shed light on the intimate roles for the 2 NOS isoforms in asthma pathobiology, and these studies should be aimed to therapeutic perspectives of cNOS activity restoration, iNOS expression reduction, or both.

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Reply

To the Editor:

Ricciardolo and Rossi¹ comment that possible explanations for our findings on the relationships of exhaled nitric oxide (eNO) to clinical and inflammatory markers² might result from the differential effects of the expressed isoforms of the nitric oxide synthases (NOSs) in the lung. eNO is the product of different concentrations of NO generated by the inducible and constitutive isoforms. They suggest that correlations between eNO and inflammatory markers are stronger than those between eNO and spirometry and airway lability tests because inducible NOS, which is thought to be proinflammatory, produces higher levels of eNO than constitutive NOS, which is thought to be bronchoprotective. We thank them for again raising these important concepts, as they have done in the past.³

The apparent paradox of moderate significant associations between eNO and inflammatory markers with poor or no relationship between eNO and spirometry values or clinical symptoms requires a more thorough understanding of the different isoforms of NOS. Recent genetic studies noting an association of variations in the *NOS3* gene in endothelial cells and constitutively expressed levels of eNO in the lungs of asthmatic patients⁴ might be helpful in future investigations in this area. Precluding these further investigations, our findings do suggest that eNO might be providing information about the asthmatic state not provided by pulmonary function tests designed to measure obstruction of airflow. Concurrent inflammation measured on the basis of eNO is more related to methacholine responsiveness than airflow obstruction, suggesting that eNO might help determine the adequacy of medication to control asthma. In this context eNO measurements were predictive in determining loss of asthma control during inhaled steroid withdrawal.⁵ Moreover, in this latter study, eNO measurements were as useful as induced sputum analysis and airway hyperresponsiveness in predicting loss of asthma control. Moreover, in accord with our suggestion, ease of measurement of eNO compared with other parameters provides an advantage in using eNO to assess airway inflammation.

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Misuse of terminology to imply that 1,25-dihydroxy-vitamin D is a nutrient: There is no evidence for an association between vitamin D and allergy

To the Editor:

Some things are so wrong, they must be quoted at length to convey the severity of the situation. This is the case with Matheu et al,¹ who open their recent article with the words "vitamin D, a common food additive." They go on to speculate whether "vitamin D-fortified food products" may be contributing to allergy among those living a "Westernized lifestyle." The study's objective was stated to investigate "the role for in vivo vitamin D in modulating development of a T_H2-mediated disease." The concluding paragraph states that the authors "provide some evidence of a possible role of vitamin D in the development of allergic disease" and that their mice were given "daily vitamin D supplement of approximately 2 µg/kg, which is in the same dose range as the Scandinavian recommendation of 10 µg/d in children weighing 5 to 10 kg. Thus ... dietary vitamin D should be considered