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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

a hormone with the potential of skewing the immune system toward T_H2 -mediated immune reactions and allergic responses.”¹ (The italics are mine to emphasize the nutrition slant of this paper.)

Some readers have expressed alarm to me about what appears to be an allergy-related aspect of vitamin D nutritional supplementation. Because they only saw the summary available on PubMed, these readers did not have the slightest hint that Matheu et al¹ had actually used 1,25-dihydroxy-vitamin D (calcitriol). This is not a nutrient but rather the potent renal hormone made from vitamin D. The authors gave 0.1 μ g of calcitriol to mice at a dose 200 times more per kilogram of body weight than what nephrologists would prescribe to anephric human beings!

Either Matheu et al were confused about what I admit is difficult terminology surrounding vitamin D² or they allowed a desire for dramatic impact of their paper to go too far. From its introduction to its conclusion, their paper is framed in nutrition-oriented words such as food additive, supplement, and dietary vitamin D. The fact that they used calcitriol is well hidden, and its use was usually substituted with the term “vitamin D.” Thus, it is no surprise that most readers have come to the wrong conclusion, that is, that the paper relates to nutrition. In reality, this is a toxicology study of a compound fundamentally different from anything we can get in food or vitamin pills.

I emphasize that contrary to the claims made in the publication, the Matheu et al study¹ is a pharmacologic study that has nothing to do with nutrition. It provides no association whatsoever between allergy and vitamin D supplementation.

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Reply

To the Editor:

We are grateful to Mr Vieth¹ for paying attention to our recent article published in *The Journal of Allergy and Clinical Immunology*.² Vitamin is a general term for a number of unrelated organic substances that occur in many foods in small amounts and that are necessary in trace amounts for the normal metabolic function of the body. “Vitamin D” is any one of several fat-soluble

compounds, known commonly as calciferol. The recommendations of International Union of Pure and Applied Chemistry and International Union of Biochemistry and Molecular Biology, based on H. F. DeLuca's and other workers' proposal, say that the term vitamin D should be used as a general term to describe all steroids that exhibit qualitatively the biological activity of calcitriol.³ Definitely, many compounds can be called vitamin D, and some of them⁴ with activity in vitamin D receptor, but either 1 α ,25-dihydroxyvitamin D₃ (1 α ,25-(OH)₂-vitamin D₃) or 1,25-dihydroxycholecalciferol or calcitriol had been a more exact term in our paper.²

Discussing the effects of vitamin D on allergic inflammation in mice,² Mr Vieth is claiming that it was not a nutritional study. We totally agree. The paper is a study of pharmacologic effects of 1 α ,25-(OH)₂-vitamin D₃ (1,25-dihydroxycholecalciferol or calcitriol), an active metabolite of vitamin D, on the immune system in mice in short-term experiments.² This was not hidden, as Mr Vieth claims. Our aim was to investigate if it is possible to interfere with the T_H1/T_H2 balance through administration of an active vitamin D-metabolite.⁵ Calcitriol, given as subcutaneous injections every second day, was used^{6,7} to control the blood levels in all mice. Furthermore, the dose 100 ng of calcitriol is taken from the mouse immunology literature, there given either as intraperitoneal injections or as special diets.^{7,8}

The possibility that vitamin D status is an environmental factor affecting the prevalence of autoimmune diseases has been published elsewhere.⁹ The other side of the coin might be that vitamin D or analogues could contribute to the development of allergic diseases. Mr Vieth claims that our study provides no association between allergy and vitamin D. We think we have clearly demonstrated that in C57BL/10 mice, which are not a common strain of mice used in allergy studies,¹⁰ calcitriol is able to increase the T_H2 response, measured as specific IgE production, as we and others have suggested before.^{11,12} Furthermore, Overbergh et al have recently reported exacerbation of anaphylactic symptoms with higher levels of specific IgE in hen egg white lysozyme-immunized NOD mice after treatment with calcitriol.

Whether dietary vitamin D,⁷ which can be converted to the active metabolite calcitriol in vivo, contributes to the development of allergy¹¹ could be addressed in properly controlled studies in human beings if nutritionists, epidemiologists, and immunologists come together. Then we will know if there is an association between allergy and vitamin D supplementation in our patients.

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