Vitamin D and Active Tuberculosis: A Futile Quest?

To the Editor:

We are grateful for the letter by Dr. Davies commenting on our editorial (1), which accompanied the article by Dr. Wesje and colleagues (2). Dr. Davies' letter adds to the discussion on the possible role of vitamin D supplementation in the immune response against *M. tuberculosis*. We respect the fact that Dr. Davies helped revive interest in this subject, but also note that the first recorded therapeutic use of vitamin D in tuberculosis dates back to the year 1849 (reviewed in Reference 3).

The mechanisms of vitamin D modulation of immune defense against *M. tuberculosis* are incompletely understood. Antimycobacterial actions of vitamin D are modulated by the active metabolite 1,25-dihydroxyvitamin D (1,25[OH]2D) and they include, among possible other mechanisms, the induction of cathelicidin LL-37, an antimicrobial peptide with documented antituberculosis activity (4, 5). As antimicrobial peptides act in the first line of innate immune defense, vitamin D deficiency could rather influence the susceptibility to human *M. tuberculosis* infection following aerosol exposure than alter the course of active tuberculosis or putative latent tuberculosis infection (LTBI). However, this hypothesis, like the alternative hypothesis proposed by Dr. Davies, has not been addressed in clinical trials.

We are also not aware of published evidence that the early introduction of antiretroviral therapy during tuberculosis therapy in HIV-infected persons has an effect on sputum conversion. Similarly, it has not been evaluated to our knowledge whether glycemic control enhances tuberculosis treatment outcome or reduces the reactivation of LTBI.

Recent epidemiological findings suggest that genetic variability of proteins involved in the vitamin D dependent metabolism are likely to influence the vulnerability of individuals with low serum levels of vitamin D to develop tuberculosis (6). While vitamin D supplementation can enhance the *ex vivo* ability of human whole blood to suppress *Mycobacterium bovis* Bacille Calmette-Guérin (BCG) bioluminescence, in an assay that tests for both innate and acquired immune responses against mycobacteria from the *M. tuberculosis* complex (7), clinical trials are still to be performed to evaluate whether vitamin D supplementation prevents *M. tuberculosis* infection or reactivation of LTBI in individuals with low serum levels of vitamin D. In addition, it needs to be ascertained whether vitamin D supplementation can improve the outcome of patients treated against active tuberculosis relating to genetic polymorphisms of proteins involved in the vitamin D dependent pathways. These clinical studies will hopefully shed more light on the role of vitamin D supplementation to augment the immune defense against primary *M. tuberculosis* infection, LTBI, and active tuberculosis.

Conflict of Interest Statement: C.L. has no financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.J.W. has received a patent on behalf of Institut Pasteur.

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Long-Term Outcomes of Acute Irritant-induced Asthma and World Trade Center–related Lower Airway Disease

To the Editor:

As a pulmonologist dedicated exclusively for almost 7 years to the diagnosis and treatment of presumed World Trade Center (WTC)–related lower airway disease (LAD), I read with interest the recent article by Dr. Malo and colleagues on long-term outcomes of acute irritant-induced asthma (IIA) (1), and have several comments related to the authors' findings and statements. WTC inhalation injury is not the best known outbreak of IIA syndrome (also known as reactive airways disease syndrome [RADS]), as stated by Malo and coworkers. In fact, most of the lower airway disease resulting from the occupational WTC dust exposure did not meet acute IIA criteria (2), and only a small proportion of cases (22.6%) met criteria for IIA altogether (3).

In the vast majority of workers, lower respiratory symptom onset was relatively delayed and insidious over weeks and months, and in some patients latency between exposure cessation and symptom onset could be up to 6 mo after leaving the disaster site. That partially explains why exposure duration could be so prolonged (mean, 18.2 wk; SD, 15.6 wk) (3, 4). Furthermore, only about 27% of the patients with LAD had evidence of nonspecific bronchial reactivity 1 to 2 years after leaving the WTC site (3), although that may partly reflect the well-known resolution or mitigation of nonspecific bronchial hyperreactivity that, as Malo and coworkers report, happens in some individuals. Other forms of irritant-induced airway disease included aggravation of probably preexistent subclinical or very mild chronic obstructive pulmonary disease, a nonspecific chronic bronchitis picture, and bronchiolitis/small airway disease (3, 5).

With regard to the observation on the role of smoking as a predisposing or additive risk factor, we also found it in our

WTC dust–exposed workers (3). The caveat for the latter is that we found it as a risk factor for all lower airway diseases, including clinical forms other than IIA. Atopic status, the third most frequently investigated risk factor for IIA (together with occupational exposure and tobacco smoking), was not reported by Malo and coworkers. We identified it as a risk factor for upper but not for lower airway disease in WTC workers (6). It would have also been informative to report on the chronic upper airway disease that frequently accompanies IIA, and contributes substantially to poor symptom control and quality of life.

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Stronger Evidence for Replication of NPPA Using Genome-wide Genotyping Data

To the Editor:

We thank the *Journal* for the opportunity to present an addendum to our article, "Assessing the Reproducibility of Asthma Candidate Gene Associations using Genome-wide Data" (1). In that work, we studied 39 replicated asthma gene regions using data from the Illumina 550kv3 genome-wide SNP genotyping platform. We reported the results of SNP-level replication within 6 genes and additional "gene-level" replication in 15 more genes. Lima and colleagues reported that the gene encoding atrial natriuretic peptide, NPPA, was associated with asthma in two populations (2), and thus their results were included in our study. We assessed 6 SNPs in NPPA, including one SNP (rs5065) which was directly tested by Lima and coworkers (2).

We found evidence of association in 3 SNPs in NPPA (two-sided $P < 0.05$); in all cases transmission of the minor allele conferred a decreased risk of asthma. We incorrectly reported that our association in rs5065 was in the opposite direction of that identified by Lima and coworkers. In fact, the minor allele for marker rs5065 (G on the + strand) was associated with decreased asthma susceptibility in both the original publication by Lima and coworkers (2) and in our study (1). Thus, our replication of the association between NPPA and asthma is more compelling than we had originally reported.

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