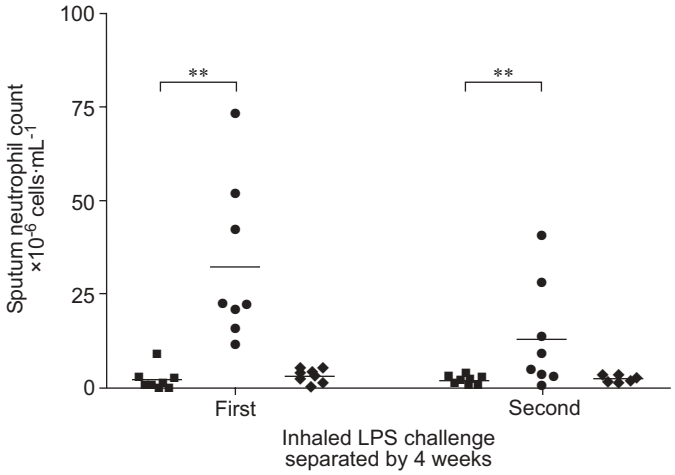

FIGURE 1. Comparison of sputum neutrophilia post-inhaled lipopolysaccharide (LPS; 6th h) between two inhaled LPS challenges separated by 4 weeks. ■: baseline; ●: 6 h post-inhaled LPD; ◆: 1 week post-inhaled LPS. **: denotes p=0.01 between the mean differences.

LPS on two occasions separated by ⩾3 weeks. However, none of these studies had observed tolerance towards subsequent LPS challenge(s) in their healthy human subjects at doses of LPS described that were higher than ours. It is possible that tolerance in healthy nonatopic human subjects only occurs in exposure to lower doses of inhaled endoxin. In fact, existing literature indicates that exposure of 30–40 μg inhaled LPS is probably the clinical threshold to induce symptoms and lung function changes for healthy subjects [4].

More research is required to validate our preliminary observation.

L.C. Loh
Dept of Medicine, Clinical School, International Medical University, Jalan Rasah, Malaysia.

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From the author:

The study that L.C. Loh describes in his letter above adds another interesting aspect that is critical for the response to inhaled endotoxin.

Lipopolysaccharide tolerance is a well-known feature of several host defence cells, although the mechanisms involved are not entirely clear [1]. Tolerance has also been shown to be associated with various cellular processes, such as decreased activity of Gi proteins, protein kinase C, mitogen-activated protein kinase, activator protein-1 and nuclear factor-κB (NF-κB). Inhibitory molecules such as IRAK-M, suppressor of cytokine-signaling-1 and inhibitor-κB are found activated. At the nuclear level, the NF-κB subunit p50 homodimer expression and peroxisome-proliferator-activated receptors-γ are increased. There is evidence from rodent studies that this phenomenon is also relevant for pulmonary innate immunity [2].

The preliminary results described in this letter support this view and it is likely that this mechanism is of biological relevance, because the lung is constantly exposed to small amounts of lipopolysaccharide. The pulmonary exposure with endotoxin probably has many consequences. At this time it is uncertain where lipopolysaccharide tolerance is functionally located in this scenario.

R. Bals
Hospital of the University of Marburg, Marburg, Germany.

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Pre-analytical conditions for the assessment of circulating MMP-9 and TIMP-1: consideration of pitfalls

To the Editors:

We read with interest the recent article of HIGASHIMOTO *et al*. [1], which reported an increased activity of tissue inhibitor of metalloproteinase (TIMP)-1 in patients with chronic obstructive pulmonary disease (COPD) and asthma. In contrast, the molar ratio between matrix metalloproteinase (MMP)-9 and TIMP-1 was significantly lower in COPD patients than in normal subjects.