Correspondence

Useful Models of Asthma Need to Properly Phenotype Airway Narrowing

To the Editor:

In the March, 2011 issue of the *American Journal of Respiratory Cell and Molecular Biology*, Fedulov and Kobzik published a paper showing maternal transfer in allergically sensitized mice of CD11c⁺ dendritic cells with altered DNA methylation (1). Although they argue that this process may be involved with the development of asthma in neonates, unfortunately the work is flawed by an overinterpretation of the functional measurement that relies solely on the empiric variable, “enhanced pause” or Penh, which has been shown to be primarily related to ventilatory timing and unrelated to airway resistance (2, 3). The consensus for the past 7 years among respiratory physicians and physiologists is that, by itself, the use of Penh is not to be trusted (4). This inability of Penh to adequately phenotype airway function was recently emphasized and confirmed in an extensive genetic association study with 29 mouse strains, which showed that Penh and airway resistance were clearly associated with different genomic regions (5).

The explanation given by the authors for using Penh is that it would be too difficult to measure pulmonary function in mice so young using an invasive method. This is an unacceptable justification for an inadequate measurement. Our concern echoes the unambiguous statement many years ago by the famous statistician John Tukey,

When the right thing can only be measured poorly, it tends to cause the wrong to be measured only because it can be measured well. And it is often much worse to have good measurements of the wrong thing (especially when, as so often is the case, the wrong thing will in fact be used as an indicator of the right thing) than to have poor measurements of the right thing. (6)

In their attempt to justify using the wrong thing, the authors cite references that “arguably” support their case. In fact these citations offer no such support. Without some mechanistic understanding and linkage, simply citing a correlation between Penh and direct measurements is no better than, say, citing a correlation between height and body weight in humans. In addition, several other references are simply included in support, even though they have nothing to do with the assumed correlation.

The seductive simplicity of the Penh measurement makes it attractive to investigators who lack the motivation and/or skill to make the proper measurement. With careful preparation, however, measurements of airway mechanical function can be made in small mice (7), and this should have been done, since without solid evidence of increased airway narrowing to Mch stimulation, the model has no relevance to asthma. The end result is that the authors spent considerable effort to show that DNA methylation of splenic dendritic cells can affect a mouse’s breathing pattern and perhaps sensitivity to inhaled irritants, a finding that might have some importance to the control of ventilation and its interaction with the adaptive immune system, but unfortunately provides little insight into the asthma pathology.

It is also of concern that this journal, which is to be commended for having the foresight to publish the consensus letter (4), seems to have overlooked the essential role that was ascribed to Penh in this recent paper (1). Insofar as the interpretation and problems with Penh have not changed, we urge the reviewers and

editors to ensure that the quantitative methodology reported in this journal adheres to high standards.

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The Penh Police Are Not Infallible

From the Authors:

Common practice in rebuttal letters calls for dry scholarship and genteel, if sometimes strained, etiquette. To make the discussion a bit more lively, we prefer to view ourselves as defendants in a science equivalent of an indictment, and we will follow what is by now a familiar legal strategy. First, we will vigorously dispute the accusations as if we were completely in the right. Next, following common practice to sway the court of public opinion, we will attempt to discredit our accusers. Finally, we will finish more gracefully with a proposed compromise that hopefully keeps us out of jail.

Our decision to use Penh measurements is based on three related arguments. First, the correlation between Penh and more invasive methods *for our experimental conditions* is sufficient to be useful (Reader: this sounds lukewarm, but