

Correspondence

Peptide Therapy and Asthma

To the Editor:

We read with interest the editorial by Boulet (1) that accompanied our recent publication in the *Journal* (2).

In his discussion of the therapeutic use of allergen-derived peptides, Dr. Boulet omits citations of findings from a number of our earlier studies that support the potential of peptide immunotherapy. Instead, he refers to earlier published data with different peptides (i.e., IPC 1 and IPC 2, which only covered chain I of Fel d 1 [3]). It is our contention that peptide therapy remains an exciting possibility. The majority of studies of peptide therapy for allergic diseases (3–7) have demonstrated some degree of clinical efficacy. It is important to pursue this avenue to refine treatment protocols and peptide preparations, thereby thoroughly evaluating the potential of the approach.

In the studies we refer to, we demonstrated the induction of isolated late asthmatic reactions (LARs) after intradermal administration of short T cell peptide epitopes from a major allergen (Fel d 1) (8). Sampling at the height of the reaction (6 hours) by bronchoscopy, we determined that LARs induced by intradermal peptide administration did not appear to be accompanied by any cellular recruitment to the bronchial mucosa or the generation of enhanced levels of mediators known to be associated with bronchoconstriction (9).

Furthermore, we also showed that intradermal administration of peptides was subsequently associated with the induction of hyporesponsiveness, both to the peptides and to the whole allergen (10). Observations in relation to the ability of peptides to induce hyporesponsiveness or “immunological tolerance” were further supported by a randomized, double-blind, placebo-controlled trial in which Fel d 1 peptide administration to cat allergens was shown to markedly modulate T cell responses *in vitro*, to significantly reduce the magnitude of both early and late cutaneous reactions to whole allergen challenge, and to improve toleration of cats (4).

Finally, we would like to shed further light on the mechanisms underlying the peptide-induced LARs. In a recent unpublished study, to analyze mucosal changes, we subjected cat allergic asthmatic subjects who were experiencing an inhaled peptide-induced LAR to bronchoscopy with endomucosal biopsy and alveolar lavage. Our results suggest that the only significant increase in cell numbers in the mucosa is in the CD4⁺ T cell compartment, and that despite the detection of mild sputum eosinophilia in the recently published study (2), eosinophils were not significantly increased in bronchoalveolar lavage or bronchial mucosa during (6-hour time point) peptide-induced LARs.

Conflict of Interest Statement: M.L. has acted as a consultant to Powderject Pharmaceuticals PLC in the field of peptide vaccine development for allergic diseases and received \$80,000 in consultancy fees from June 2002–present; he is a coinvestigator on a grant from Powderject Pharmaceuticals PLC with a value of approximately \$800,000, and received approximately \$160,000 after the sale of Powderject Pharmaceuticals PLC to Chiron Vaccines; A.B.K. has acted as a consultant to Powderject Pharmaceuticals PLC in the field of peptide vaccine development for allergic diseases and received \$106,000 in consultancy fees from June 2002–present; he is a coinvestigator on a grant from Powderject Pharmaceuticals PLC with a value of approximately \$800,000, and received approximately \$300,000 after the sale of Powderject Pharmaceuticals PLC to Chiron Vaccines.

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From the Author:

I would like to thank Drs. Larché and Kay for their comments on my editorial about their recent study on late asthmatic reactions induced by inhalation of allergen-derived T cell peptides, and, in particular, for providing additional information and some unpublished data on this matter (1, 2).

It is not possible to make an exhaustive review of the topic in the limited space of an editorial. I therefore chose to report what I considered some of their previous key observations on intradermal administration of peptides and mostly focus the discussion on the effects of inhaled peptides (2–4).

I can understand their enthusiasm about the possibilities of peptide therapy, but they also admit that its clinical efficacy has been up to now relatively modest. I nevertheless did stress in my editorial that “future studies are needed to further explore this important field of research,” although their data showed that the inhaled route has some limitations that could make this route of administration unsuitable for such treatment.

In the study reported by Oldfield and coworkers (5), multiple injections of T cell peptides derived from Fel d 1 to patients allergic to cats led to a reduction in early- and late-phase allergic reactions to whole allergens and modulated the production of interleukin (IL)-4, IL-10, IL-13, and INF- γ by peripheral mononuclear cells (5). However, although it does not exclude a possible benefit, improvement in patients’ subjective ability to tolerate exposure to cats was not different compared with the placebo. In regard to the unpublished data provided, it is certainly most

interesting and I look forward to reading about this interesting study.

I therefore agree that various observations, including many coming from the group of Drs. Larché and Kay, whom I acknowledge as having made a major contribution to this field, show that peptide therapy can modulate immune responses to peptides and allergens. However, the clinical significance of these observations and the exact role of peptide immunotherapy remain to be determined.

Conflict of Interest Statement: L.-P.B. has served as an advisor and participated in educational and research activities of most pharmaceutical companies involved in asthma care and to various national respiratory societies and governmental committees.

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1. Boulet L-P. Allergen-derived T cell peptides and late asthmatic responses. *Am J Respir Crit Care Med* 2004;169:2-3.
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5. Oldfield WL, Larché M, Kay AB. Effect of T-cell peptides derived from Fel d 1 on allergic reactions and cytokine production in patients sensitive to cats: a randomised controlled trial. *Lancet* 2002;360:47-53.

Renal Function in Critically Ill, Morbidly Obese Patients

To the Editor:

We appreciate the Clinical Commentary by Dr. El Solh concerning critically ill, morbidly obese patients (1). The evaluation of renal function in such patients seems of importance and was not mentioned. Hypertension, diabetes mellitus, and other current complications of being overweight may severely compromise renal function (2). Glomerular hyperfiltration, hyperlipidemia, leptin, and adipocyte-derived hormone play critical roles in the development of focal and segmental glomerulosclerosis (FSG) (3). The long-term prognosis of obese patients with biopsy-proven FSG is poor, with almost one half ultimately experiencing development of advanced renal failure. The management of such patients, with frequently impaired renal function, may require dose adjustment especially for low molecular weight heparins, iodine contrast media, and drugs excreted by the kidneys. The glomerular filtration rate (GFR) is traditionally considered the best over-

all index of renal function. Most clinicians estimate the GFR from the serum creatinine concentration (SCr). However, the accuracy of this estimation is limited because the SCr is affected by factors other than GFR. No formula is more widely used than that proposed by Cockcroft and Gault (4). More recently, the Modification Diet in Renal Disease (MDRD) Study Group proposed a new formula, including SCr, sex, age, and ethnicity (black or others): $214 \times [\text{SCr, mg/dL}]^{-0.113} \times [\text{age, years}]^{-0.174} \times [0.762 \text{ if patient is female}] \times [1.180 \text{ if patient is black}]$ (5). The GFR is expressed in ml/minute per 1.73 m^2 . This model has been validated in 1,628 patients whose main weight was $79.6 \pm 16.8 \text{ kg}$. In opposition to the Cockcroft and Gault formula, it does not include the weight and may be less reliable in obese patients. Indeed, after correction for surface body area, using the Dubois and Dubois formula, it seems more accurate for determining obesity. Data obtained in an intensive care unit of a morbidly obese patient are summarized in Table 1, using I^{51}Cr -ethylenediamine tetraacetic acid clearance as the gold standard. In Figure 1, we evaluate an example for different values of creatinine, using the two formulas. The Cockcroft and Gault formula doesn't seem of value in obese patients, overestimating the GFR. We thus believe that MDRD has to be used in the critically ill morbidly obese patient.

Conflict of Interest Statement: F.V. does not have a financial relationship with a commercial entity that has an interest in the subject of this letter; N.E.-K. does not have a financial relationship with a commercial entity that has an interest in the subject of this letter; E.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this letter.

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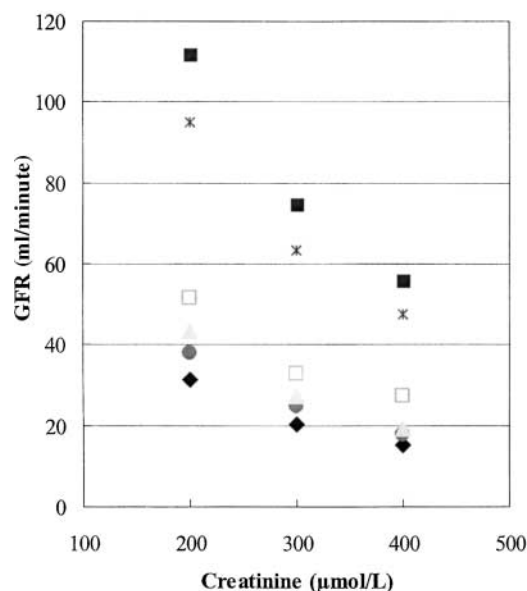


Figure 1. Examples of predicted glomerular filtration rate (GFR) from serum creatinine using the modification diet in renal disease (MDRD) (5) or Cockcroft and Gault (2) formula. Age, 60 years; weight, 130 kg; height, 170 cm; body mass index, 45 kg/m^2 . Asterisk = Cockcroft and Gault woman; circles = MDRD black woman; diamonds = MDRD white woman; filled squares = Cockcroft and Gault man; open squares = MDRD black man; triangles = MDRD white man.

TABLE 1. GLOMERULAR FILTRATION RATE ESTIMATED IN A CRITICALLY ILL OBESE PATIENT

	Cockcroft and Gault	MDRD	I^{51}Cr -EDTA clearance
ml/minute/ I^{51}Cr -EDTA	101.8 + 84%	54.88 + 0.7%	55.3

Definition of abbreviations: I^{51}Cr -EDTA = iodine⁵² creatinine-ethylenediamine tetraacetic acid; MDRD = modification diet in renal disease.

The patient has the following characteristics: height, 146 cm; weight, 131 kg; body mass index, 61.5 kg/m^2 ; creatinine, 119 μmol/L .

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From the Author:

I thank Dr. Vincent and his colleagues for their insightful comments regarding my recent Clinical Commentary (1). Creatinine clearance is considered the most practical measure of glomerular filtration rate (GFR) in hospitalized patients. Although inulin clearance represents the gold standard for measuring GFR, it is both costly and labor intensive making it impractical in clinical settings. Numerous formulas and nomograms have been devised on the basis of age, sex, body surface area, and serum creatinine concentration to estimate creatinine clearance (2–4); however, none of these derived equations has been proven accurate in critically ill, morbidly obese patients when compared with measured creatinine clearance obtained by 24-hour urine collection (5). The new prediction formula derived from the Modification Diet in Renal Disease (MDRD) Study Group (6) has the advantage of predicting GFR rather than creatinine clearance, can be readily calculated from available demographic variables, and seems more accurate than the other equations. Nonetheless, the performance of the MDRD study equation has not been validated in critically ill, morbidly obese patients across the spectrum of renal function. The equation may vary with conditions that interfere with creatinine secretion (e.g., cimetidine) or creatinine assay (e.g., diabetic ketoacidosis) and may be inaccurate in patients not in steady state of creatinine balance. The data provided by Dr. Vincent and coworkers are promising, but pending a larger comparative prospective study, measurement of creatinine clearance by 24-hour urine collection should not yet be abandoned.

Conflict of Interest Statement: A.E-S. does not have a financial relationship with a commercial entity that has an interest in the subject of this letter.

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1. El-Solh AA. Clinical approach to the critically ill, morbidly obese patient. *Am J Respir Crit Care Med* 2004;169:557–561.
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More Respect for Respiratory Variation in Arterial Pressure

To the Editor:

We read with interest Dr. Magder's Clinical Commentary on the respiratory variations in arterial pressure (1). We would like to address the following comments.

Prior studies have clearly demonstrated that respiration has complex effects on the filling and emptying of the right and left ventricles. Thus, it is somewhat surprising that Dr. Magder did not mention the effects of respiration on pulmonary circulation, ventricular interdependence, cardiac compliance, and pulmonary transit time. As a result, Dr. Magder ignored numerous prior contributions constructively addressing the physiologic basis of arterial pressure variation. We believe that only the rational analysis of the subtle heart–lung interactions helps to understand why stroke volume variation and hence arterial pressure variation give a reliable prediction of fluid responsiveness (2, 3). We also have great reticence to rely on the superposition of venous return and cardiac function curves (see Figures E2–E4, E6–E8, E10, and E13 in the online supplement to the Clinical Commentary) in explaining the physiologic determinants of the respiratory variation in arterial pressure. This framework may be useful to describe cardiac physiology under steady state conditions. However, we do not believe that this framework can be used to explain the transient effects of mechanical insufflation for at least two reasons: (1) the pulmonary circulation appears as a rigid tube interposed between the right atrium and the left ventricle, and this is not a tenable view, especially when respiratory changes in stroke volume are discussed; and (2) the transmural central venous pressure (the x axis of the cardiac function curve) and the intramural central venous pressure (the x axis of the venous return curve) do not vary in the same direction during mechanical insufflation: the transmural pressure decreases, whereas the intramural pressure increases.

Dr. Magder raised doubts about the rationale for using the pulse pressure instead of the systolic pressure variation to predict fluid responsiveness (1). The pulse pressure depends on stroke volume and on arterial compliance (4); the systolic pressure depends on stroke volume, arterial compliance, and diastolic pressure (systolic pressure = pulse pressure + diastolic pressure). Therefore, from a physiologic point of view, pulse pressure is more closely related to stroke volume than systolic pressure. Furthermore, from a clinical point of view, pulse pressure variation works better than systolic pressure variation to predict fluid responsiveness (2, 5).

Finally, the respiratory variation in arterial pressure has been validated as a predictor of fluid responsiveness only in mechanically ventilated and deeply sedated patients. No need to say that this may limit the clinical usefulness of pulse pressure variation in intensive care units (ICUs), as clearly indicated in previous studies (2, 3). Importantly, this limitation does not apply to most operating room patients, by far the largest field of application of this clinical tool. Predicting fluid responsiveness is a relevant question in patients with acute circulatory failure in whom we believe that increasing cardiac output could be beneficial. Fortunately, “most of ICU patients with acute circulatory failure are sedated and receiving mechanical ventilation” as stated a few years ago by Dr. Magder (6) when discussing the limitations of the inspiratory decrease in central venous pressure as a tool to predict fluid responsiveness. Although there is a trend in using a lower level of sedation during mechanical ventilation, the accurate assessment of respiratory mechanics (e.g., the measurement of airway plateau pressure or total positive end-expiratory pressure) frequently requires sedation, at least transiently. In this regard, Morelot-Panzini and colleagues (7) proposed to combine

the analysis of arterial pressure variation with the evaluation of respiratory mechanics. This approach should extend the clinical usefulness of the respiratory variation in arterial pressure to most mechanically ventilated patients.

Conflict of Interest Statement: F.M., D.C., and J.-L.T. do not have a financial relationship with a commercial entity that has an interest in the subject of this letter.

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References

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From the Author:

I thank Dr. Michard and coworkers for their comments on my article (1). I fully agree that respiration has “complex effects” on the filling and emptying of the ventricles; however, my task was not to give a comprehensive analysis of this complex interaction, but rather to explain the phenomenon of arterial pulse variation and how it is affected by volume status. Too often authors describe all possible factors that impact on a phenomenon, many of which have only minimal quantitative effects, and truly important factors are not made clear. This confuses the audience and fails to give meaningful mechanisms. In their articles, Dr. Michard and coworkers described many aspects of heart–lung interaction but never actually explained how these processes produce the respiratory variations in arterial pressure or why the phenomena is volume responsive. My explanation does so very satisfactorily.

Dr. Michard and coworkers raise two problems with the venous return–right heart interaction analysis. The first is that it does not account for pulmonary compliance and effect of changes in lung volume. In a classic article, which is not often quoted, Scharf and colleagues (2) showed that the increase in pleural pressure rather than the increase in transpulmonary pressure is the primary determinant of the decrease in cardiac output with positive-pressure ventilation (2). Furthermore, Denault and colleagues (3) showed that opening the chest removes respiratory variation in left ventricular volume and arterial pressure without

a change in tidal volume. Thus, I based my analysis on the assumption that the change in pleural pressure is the *dominant* factor.

The second criticism was that the venous return–cardiac function analysis does account for changes in transmural pressure. It certainly does. The movement of the cardiac function curve relative to the atmospheric reference point accounts for this.

I agree with Dr. Michard and colleagues that pulse pressure was a better indicator in one study than the systolic pressure variation, but *dDown* (fall in pressure relative to end-expiratory value) really should be most representative of the fluid-responsive component, and this is likely better reflected in the pulse pressure change.

Before writing my clinical perspective, it was not obvious to me that the proposed tests are *only* valid in patients with no respiratory effort, and I suspect that it was not obvious to others. The intensive care unit at my institution rarely has patients with no respiratory effort. Furthermore, even when studying patients in the operating room, which Dr. Michard has not done, differences in tidal volume, aortic compliance, peripheral resistance, and even abdominal pressure have important effects on quantitative predictions on the basis of respiratory variations in arterial pressure.

I believe that Michard and coworkers need to have more respect for the limitations of these tests.

Conflict of Interest Statement: S.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this letter.

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Respiratory Variations in Arterial Pressure

To the Editor:

I read with amused interest Dr. Magder’s recent Clinical Commentary (1).

To explain respiratory variations in arterial pressure, in particular, in mechanically ventilated patients, Dr. Magder uses a simple description of the central circulation that was proposed by Guyton in the 1950s: the heart is a pump with two chambers, the right atrium, which receives the venous return, and the left ventricle, which is responsible for cardiac flow and whose ejection volume determines arterial pressure, all else being equal. This description, which has the merit of simplicity, allows the beautiful illustration that embellishes the cover of the January 15, 2004 issue of *AJRCCM*, where phenomena involving the right atrium and venous return are colored blue, and red is used for phenomena concerning the left ventricle and arterial pressure.

We need to retrace the path of evolution a long way to find a species to which this description applies perfectly: fish. But in humans, is there nothing between the right atrium and the left ventricle? Or is the pulmonary circulation, which starts with the right ventricle and ends with the left atrium, a simple rigid tube, completely insensitive to changes in airway pressure?

In an irresistible flash of humor, Dr. Magder invites us to

practice a volume expansion among readers of the "Blue Journal." After such a stressful experience, we should scarcely be surprised if most of them suffer a rise in cardiac flow! An unnecessary stress what's more, because these good readers have asked nothing of anyone and have not the slightest need of an increased cardiac flow. In fact though, I don't think that they run the risk of worrying hemodynamic instability, not even on reading Dr. Magder's Clinical Commentary!

Conflict of Interest Statement: F.J. does not have a financial relationship with a commercial entity that has an interest in the subject of this letter.

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Reference

1. Magder S. Clinical usefulness of respiratory variations in arterial pressure. *Am J Respir Crit Care Med* 2004;169:151–155.

From the Author:

I appreciated Dr. Jardin's amused interest in my recent Clinical Commentary (1). His observations have been very important for understanding heart–lung interactions, and I reviewed his work in detail when I prepared my article. His criticism is cryptic, but I will attempt to elucidate it.

Dr. Jardin emphasizes that the pulmonary circulation sits between the right and left hearts, and that lung inflation can significantly alter right ventricular output. This important concept is often neglected and can lead to faulty reasoning. For example, it has been argued that the rise in cardiac output in sepsis is due to a decrease in systemic vascular resistance and decreased left ventricular afterload. However, pulmonary vascular resistance usually rises in sepsis, which increases right ventricle afterload and makes the effect on the left heart irrelevant (2).

On the basis of elegant echocardiographic observation that showed an increase in right heart size in association with a simultaneous decrease in tricuspid inflow during lung inflation, Dr. Jardin has argued that lung inflation during normal tidal breaths has a greater effect on right heart output than the associated rise in pleural pressure, whereas I argue that the change in pleural pressure is more important. There are two problems with his argument. First, Denault and colleagues (3) found that respiratory variations in arterial pressure with lung inflation are not present when the chest is open, and pleural pressure does not change. Second, although a change in load on the right ventricle could explain an inspiratory fall in right ventricular stroke volume, it does not explain why volume status affects the response.

Why might echocardiographic observations be misleading? First, there is a question of magnitude. The size of the effect of lung inflation on the right heart is dependent on the magnitude of the change in transpulmonary pressure. With current standard tidal volumes, the effect should be small, yet the change in pleural pressure is still large relative to the gradient for venous return. Second, the volume status is critical. The right heart can adapt to increases in afterload through the Frank-Starling mechanism when the heart is on the responsive part of the cardiac function curve, but not when it is on the plateau of the function curve, in which case lung inflation could decrease right heart output.

A third factor is the resolution of echocardiography. Three frequencies interact in this analysis: respiratory rate, heart rate, and sampling rate of the device or operator, all of which make precise timing of events very limited. Perhaps this explains some fishy conclusions!

Conflict of Interest Statement: S.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this letter.

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1. Magder S. Clinical usefulness of respiratory variations in arterial pressure. *Am J Respir Crit Care Med* 2004;169:151–155.
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Interrupter Resistance and Wheezing at 4 Years

To the Editor:

Without wishing to disparage the huge effort that has gone into collecting the data described by Brussee and coworkers (1) in the recent study of 4-year-old children, I wish to comment on the exaggerated claims that the authors make for its relevance.

To summarize, the authors have demonstrated that in those 4-year-old children whose wheezing has persisted since early infancy, airway resistance measured by the interrupter technique (Rint) is 14% greater (or 0.5 SD units greater) than in those who had never wheezed. The difference was independent of the presence or absence of atopy, and we are told that adjustment for a range of potential confounders did not alter the result (although no data to substantiate this claim are given).

One might ask the simple question: if a group of healthy individuals of any age is compared with a group with persistent wheeze, 34% of whom had respiratory symptoms within the previous fortnight, would it be surprising to find a difference in airway function? If these data are to have any clinical value as a diagnostic or predictive tool, we need to know the sensitivity and specificity of Rint in differentiating healthy children from those with persistent wheeze; and more importantly, we need to be given information on the bronchodilator response of these children. It would then be possible to make a reasonable claim that lung function measurements at the age of 4 years can help to differentiate significant asthma from transient airway dysfunction.

It is surely not too much to ask that any epidemiologic data that are designed to shed light on the natural history of asthma should attempt to record postbronchodilator lung function, as well as prebronchodilator values.

Conflict of Interest Statement: M.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this letter.

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Reference

1. Brussee JE, Smit HA, Koopman LP, Wijga AH, Kerkhof M, Corver K, Vos APH, Gerritsen J, Grobbee DE, Brunekreef B, et al. Interrupter resistance and wheezing phenotypes at 4 years of age. *Am J Respir Crit Care Med* 2004;169:209–213.

From the Authors:

We agree with Dr. Silverman that it might be expected to find differences in airway resistance between healthy young children and children with persistent wheeze. However, although previous studies have shown elevated Rint values in preschool chil-

dren with physician-diagnosed asthma (1) and children referred to hospital because of wheeze (2), few studies have investigated the usefulness of Rint in discriminating between symptomatic and asymptomatic children from the general population (3). Irrespective of Rint being elevated in children with physician-diagnosed asthma, it would not be a potential diagnostic tool as long as it cannot discriminate between symptomatic and asymptomatic children in the general population, because these are the children in whom Rint could contribute to establish the diagnosis of asthma. The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study is one of the first large-scale epidemiologic studies showing elevated Rint values in symptomatic preschool children from the general population (4).

However, this does not necessarily imply that Rint is useful as a diagnostic tool. Therefore, the sensitivity and specificity of Rint in diagnosing asthma will be investigated prospectively in the PIAMA study.

We agree that children are more likely to have elevated Rint values if they had respiratory symptoms in the 2 weeks before Rint measurement. However, because recent respiratory symptoms are part of the persistent wheezing phenotype, excluding these children from the analysis would mean excluding children from the more severe part of the spectrum. Moreover, these children only partly explain the higher mean Rint values in children with persistent wheeze (mean Rint value in persistent wheezers, after exclusion of those with recent respiratory symptoms: $1.04 \text{ kPa} \cdot \text{L}^{-1} \cdot \text{second}$, $p < 0.05$ as compared with never and early wheezing phenotypes).

Indeed, adjustment for potential confounders did not alter the results of the analyses (adjusted mean Rint value in total study population after adjustment for potential confounders: $1.06 \text{ kPa} \cdot \text{L}^{-1} \cdot \text{second}$, $p < 0.05$ as compared with never and early wheezing phenotypes).

We entirely agree with Dr. Silverman that assessment of prebronchodilator and postbronchodilator Rint values would have been extremely important, and it was part of our original protocol. Unfortunately, the medical ethics committees involved in the evaluation of the study protocol did not allow studying this in healthy children from the general population.

Conflict of Interest Statement: J.E.B., H.A.S., A.H.W., M.K., K.C., and J.C.d.J. do not have a financial relationship with a commercial entity that has an interest in the subject of this letter. P.J.F.M.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this letter; he received €500 in 2003 for speaking at a Roche-sponsored meeting, and €300 for participating in an AstraZeneca-sponsored postgraduate course in 2004.

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Repeatability of Spirometry

To the Editor:

I would add one caveat to the conclusion that Enright and colleagues (1) reached that, with regard to spirometry, “the ability to meet or exceed repeatability goals depends largely on the skill and perseverance of the technician and very little on patient characteristics.” Testing needs to be performed in good faith. This is not always the case in applicants who are applying for worker’s compensation or Social Security disability benefits. In those circumstances, even the most experienced, persistent, and competent technicians are often unable to obtain three reproducible spirometry tests. The failure to meet or exceed repeatability goals in these circumstances does indeed depend on patient characteristics. This problem is more common than generally recognized.

Conflict of Interest Statement: S.A.L. does not have a financial relationship with any commercial entity that has an interest in the subject of this letter.

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Reference

1. Enright PL, Beck KC, Sherrill DL. Repeatability of spirometry in 18,000 adult patients. *Am J Respir Crit Care Med* 2004;169:235–238.

Dr. Paul Enright was given the opportunity to respond to this letter but declined to do so.

Number of Drugs to Treat Multidrug-resistant Tuberculosis

To the Editor:

We read the comments by Drs. Caminero and de March and the response by Dr. Iseman (1) with great interest. Although Caminero and de March correctly note that the optimal number of drugs used in a retreatment regimen for multidrug-resistant tuberculosis (MDR-TB) has never been studied in a clinical trial, we agree with Dr. Iseman’s opinion that a successful retreatment regimen should include four to six drugs, and not less, as Caminero and de March argue.

Our experience is with approximately 2,000 patients with MDR-TB in Peru over the last 8 years, which constitutes the largest MDR-TB patient cohort to date. In reviewing treatment histories, we have found that the most common mistake in the medical management of these patients has been the prescription of weak retreatment regimens: most patients were referred to us after failing to respond to regimens that added one, two, or three second-line drugs to a failing first-line regimen. A similar finding was reported at the chief MDR-TB referral center in the United States by Mahmoudi and Iseman (2), who classified undertreatment as a physician error. Caminero and de March are correct that the use of four, six, or more drugs will lead to greater toxicity, but our experience has shown that adverse reactions can be controlled, as Iseman suggests, even in resource-poor settings (3). Although physicians with less experience in the treatment of drug-resistant TB may be reluctant to prescribe

four to six drugs because of fears of drug toxicity, it is patients and their families who are, in the end, the most adversely affected by the use of inadequate treatment regimens.

When treating patients with MDR-TB, we recommend using at least the number of drugs used for treating drug-sensitive TB (four in the World Health Organization–recommended Category 1 regimen). In addition, directly observed therapy, aggressive management of adverse effects, rigorous drug susceptibility testing, adjuvant resective surgery, and any other treatment options that are available to the patient should be considered, because retreatment regimens are often the only hope for cure of this disease (4).

Experience in Peru, Haiti, and Russia has taught us deep respect for *Mycobacterium tuberculosis* and its ability to survive and evolve in the face of even the best-laid therapeutic plans. Caminero and de March cite studies from the National Jewish Hospital in the 1960s, where researchers reported relapse rates as high as 20.5% after culture conversion with a three-drug regimen (5). We suspect our distinguished predecessors were not satisfied with these outcomes and hope that others engaged in responding to MDR-TB feel similarly chastened.

Conflict of Interest Statement: K.J.S., K.J., R.H., M.R., S.S., J.F., F.L., J.M., and P.F. do not have a financial relationship with a commercial entity that has an interest in the subject of this letter.

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From the Authors:

Seung and colleagues write in relation to their experience in Peru, but control of tuberculosis in Peru was chaotic in the 1980s. For this reason, Peru currently has one of the worst multidrug-resistant tuberculosis (MDR-TB) situations in the world. But this is not the general situation. A lot of patients with MDR-TB

in many countries have only received first-line drugs and/or quinolones. Most of these patients can be cured if three good, previously unused drugs are selected. I could accept the administration of four drugs in the initial phase of this retreatment, to standardize management, but six or more drugs are too many, even for patients who have received many second-line drugs in the past. The problem is more a question of selection of drugs than the number of drugs. A detailed history of drugs taken in the past is pivotal in the correct selection of drugs to be used in current treatment. The problem of giving an excessive number of drugs is not only the difficult and expensive management of the side effects (Peru has the technical and economical support of Partners in Health), but the probable higher tendency to abandon the treatment when patients improve, a topic never addressed in these studies.

Seung and colleagues have found that the most common mistake in the treatment of patients who do not respond to regimens is the addition of one, two, or three second-line drugs. However, they must perform in-depth analyses of these data, as all the doctors working with MDR-TB recognize the hidden monotherapy as the most important mistake. This statement could be certain even if only two weak drugs are added; but it does not hold true with the addition of three new drugs (1–4) or two effective drugs (5). The administration of three new drugs could never be considered a physician error, because in that case the professors who wrote the 1965 (1), 1966 (1), and 1994 (2) American Thoracic Society recommendations, the 1990 British Thoracic Society guidelines (3), and the 1988 International Union against Tuberculosis and Lung Disease recommendations (4) also made this important error, and they cannot be considered inexperienced physicians. Even among the 1960s National Jewish Hospital publications, a relapse rate of 4% was reported (6), which is very close to other reports from the United Kingdom, Africa, Spain, Poland, and Czechoslovakia, all of which used only three drugs and are reviewed in our letter (1).

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