chronic obstructive pulmonary disease—a patient population the authors are particularly interested in. Their pragmatic approach would have little chance of detecting this type of behavior. Instead, it would generate a single rate constant plus a Taylor's series approximation to the unconsidered compartments. We conclude that a statistically superior and more comprehensible model of xenon washin and washout is not yet at hand.

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Reply

It appears that Dr. Williams has misunderstood the aim and scope of our paper (*1*), relative to what we consider to be primary and secondary points of importance: the equilibrium count rate (N_∞) and the exponential rate constant (k) are the essential parameters to be determined, not manipulated; all other parameters could be termed additional.

Dr. Williams states as his opinion that the improvement of fitting is due to the increased number of parameters included in the fit, and he is not surprised that the seven-parameter fit gives better results than the simple method. Apart from the fact that, in general, increasing the number of parameters does not necessarily improve the result of a fitting procedure, we expected it to do so. The question, however, is not whether it is better, which would be a qualitative question, but rather the quantitative problem of how much better it is: in which cases does the method give more reliable results for the clinically important parameters? Solving this problem requires comparing the results of different methods, and that is what we did.

With respect to the comparisons, Dr. Williams does not feel that we gave the alternative forms of analysis an equitable trial because (a) they contain fewer parameters (in fact two; not one), and (b) these parameters are not determined by a least-squares algorithm. Here he again confuses the importance of the various parameters. The results to be compared are: equilibrium count rate (N_∞) corresponding to regional lung volume, and the exponential rate constant (k) corresponding to regional specific ventilation. From these two the regional ventilation can be obtained. To make a comparison possible, the results of the different methods have to be "translated." We selected a comparison in terms of k, though it could also have been done in terms of the other indices (half-time, mean transit time, or first moment). All the methods used, including the seven-parameter method, are essentially first-order methods, and as such are comparable. It does not matter how the relevant parameters are obtained: least-squares fitting is not per se better than other approaches.

Dr. Williams' remarks concerning the moments method are not entirely clear to us. We stated that the moments method has been applied only to the washout part of the curve, so his remarks regarding the inhalation part of the curve are not applicable. Also, we did not imply that N(t) was the distribution of clearance times. Furthermore, at the beginning of washout our subject is switched from xenon inhalation to room air. This procedure can be considered as applying a step function to the region of interest, which is mathematically equivalent to bolus injection to that region.

Dr. Williams' suggestions put forward for the drawing of more valid conclusions are interesting, but they throw no new light upon the problem. The use of the same numerical, rather than statistical, optimization technique sounds attractive but the comparison is then carried out in terms of goodness of fit. We cannot see that that should be more valid than our approach, which takes simulation curves based upon literature data for the uptake of xenon in the body (*2*), inserts values for N_∞ and k, carries out the various calculations, and looks to determine whether the input values are recovered. This is a straightforward method, and valid conclusions can be drawn from it. From our comparison a conclusion can also be drawn about the validity of the simple methods.

Concerning the interpretation of the model, Dr. Williams is incorrect in not recognizing that the additional Taylor's series expansion in our method is related to background originating from extrapulmonary tissues (chest wall). The parameters a_0, a_1, and a_2 give a phenomenological description of that background, necessary because the background in xenon-133 washin and washout curves is not constant during the procedure and differs from patient to patient. With our method one can correct for such a background without measuring the xenon uptake in extrapulmonary tissues, which would take a long time. The other additional parameters, T_0 and T, are required only because of their large influence upon the goodness of fit. As yet we assign no physiological meaning to these parameters.

As we have mentioned already, all methods we considered are first-order methods, that is, they give a value (exponential rate constant, half-time, first moment, mean transit time) that can be interpreted as a first-order estimate of the distribution of clearance times in the pulmonary region of interest. It is indeed a very important question whether this distribution should not be characterized by more than one parameter. This, however, was beyond the scope of our paper, and our method has no pretensions in that direction.

Regarding patients with chronic airflow obstruction, it is most likely that they have a disturbed distribution of clearance times. That is usually reflected in the first-order estimate as a lower k, respectively higher half-time, mean transit time, or first moment.

Our method has shown that these lower values of k are determined reliably. This outcome has been confirmed in our patient studies.

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