TABLE 1. WITHIN-ASSAY (% CVw) AND BETWEEN-ASSAY (% CVb) COEFFICIENTS OF VARIATION FOR DUPLICATE RUN (MEAN ± s.d.)

Control sera	T_4		T_3		Digoxin	
	% CVw	% CVb	% CVw	%CVb	% CVw	%CVb
Low	4.4 ± 1.2	5.3 ± 1.6	5.5 ± 0.6	8.3 ± 1.4	3.2 ± 1.0	4.3 ± 1.7
Medium	3.3 ± 0.8	3.5 ± 1.0	3.8 ± 1.1	6.0 ± 1.1	2.8 ± 0.4	3.9 ± 0.7
High	3.5 ± 0.7	4.6 ± 1.5	3.3 ± 0.7	5.4 ± 1.5	3.8 ± 0.8	5.4 ± 1.8

no additional data can be given for making comparisons. The data shown represent mean values obtained from the last 10-mo period, using the same three control sera as in our previous study. The CVw and CVb were determined every month for digoxin and T_4 assays (on the average, about 25 assays per month) and every 2 mo for T_3 assays (about 24 assays per 2 mo), and they represent the variation one should expect if this instrument is used to run assays in duplicate.

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On the Improvement of Analyses of Xenon-133 Lung Washin and Washout Curves

The recent article by van der Mark et al. (*1*) claims to describe an improved method for analyzing Xe-133 lung washin and washout curves. This method involves a "pragmatic" approach whereby a human lung histogram is described as a sum of a single exponential function and an approximation of a quadratic Taylor's series expansion for residual exponentials (*2*). Justification of the use of Taylor's series is based upon the difficulty of fitting more than one exponential function to physiological curves obtained from a region of interest. It is our opinion that the improvement of fitting seen with their exponential plus polynomial model is more directly attributable to the increased number of parameters available in that case. The authors, in fact, use seven adjustable constants in fitting their pragmatic picture to both simulated and patient data. These constants include the time the fit began (T_0), the time of equilibrium concentration (T), and the required three Taylor's series multipliers: a_0, a_1, and a_2. In addition, equilibrium count rate (N_∞) and the exponential rate constant (k) were also available for manipulation. These seven values were determined simultaneously by a minimization of the reduced χ^2 statistic.

By way of contrast, three of the four alternative forms of analysis described in the article depend upon only a single parameter. Moreover, this parameter is not determined by a least-squares algorithm but by a simplistic analysis of the pulmonary histograms. For example, in the $t_{1/2}$ method, the authors measure the time to reach $\frac{1}{2} N_\infty$. This result is inverted and multiplied by ln2 to define a "rate constant." Understandably, the result, in the case of the simulation-curve comparison, is a relatively poor fit compared with that of the pragmatic seven-parameter model.

A second example of the type of simplistic alternative analysis cited by the authors can be seen in their consideration of the moments method (*3*). They state that a first temporal moment of clearance times is given by

$$M_1 = \frac{\int tN(t)dt}{\int N(t)dt},$$

where N(t) is the histogram. Since no limits of integration are included, the exact meaning of the equality is uncertain. This calculation appears, however, to be based upon the assumption that N(t) is the probabilistic distribution of Xe-133 lung clearance times. Because of the inhalation of xenon over an extended period of several minutes, N(t) actually represents the net result, in a given region of interest, of concurrent inflow and outflow. It is most certainly not the distribution of clearance times—unless a very sharp bolus injection of xenon was delivered to the region in question. Mathematically, N(t) is better represented as the convolution of the distribution of transit times with the inhaled curve of xenon presented to the lung volume. Finally in this example, the authors assume that the inverse of M_1 is a rate constant comparable to the (k) rate constant of their seven-parameter model. This last step is, again, an assumption that need not be the case (*4*). As a consequence the moments method appears to be the least desirable of any alternative model investigated by van der Mark et al. (*1*).

Similar ad hoc manipulations occur for the height-over-area method and when a single exponential curve is fitted, by least squares, to the washin segment of the histogram. This last alternative is merely a subset of their pragmatic approach and thus expected to be a relatively worse approximation to the fitting of any regional curve.

Minimally, the authors should use somewhat more realistic models having a similar number of parameters as their proposed functional representation. Second, the fitting should be done, in all cases, with the same statistical optimization technique. One could then, at the termination of the algorithm, compare the goodness of fit and draw more valid conclusions. While their model is clearly superior to simplistic analyses, it is not necessarily an improvement in any statistical sense of the word. For example, we are not given reduced χ^2 values for any of the four alternative representations of the histograms.

A question can also be raised as to the ultimate interpretation of their model. While most observers would agree that multiple exponentials are difficult to determine by any algorithm, at least the comprehension of the resultant rate constants is somewhat more straightforward than that of a set of Taylor's series coefficients. As the authors remark, their series expansion is, effectively, a sum over all other exponentials not explicitly considered in their analysis. Thus in their case the description of the patient's histogram is being forced *a priori* into a single-exponential format. The lung volume under observation, however, may contain more than one population of alveoli, so that more than one exponential function would be required in a first-order compartment model. This type of behavior is, in fact, not unexpected in victims of

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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