

human societies attach to it. As biocultural beings, humans have and will continue to evolve largely in response to their own self-created environment. For this reason, it seems prudent to try to understand features of human dietary behavior and health in as broad a context as possible.

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Use of compartmental analysis as a gold standard to compare against other methods for assessing fractional zinc absorption

Dear Sir:

In the article by Lowe et al (1), several experimental methods for assessing fractional zinc absorption (FZA) were compared in 6 women. A rigorous evaluation of the validity of the different experimental techniques is long overdue and we congratulate the authors for their attempt to clarify the issues concerning the various methods being used in different laboratories. The performance of each method was analyzed in relation

to the results of a compartmental model, developed and reported on previously (2), that used the same experimental data. Although we read Lowe et al’s article with interest, several issues need clarification.

The incorporation of 3 types of data (fecal, urinary, and plasma) was used as the justification for choosing the compartmental model as the gold standard to compare against other methods that used only one set of data (fecal, urinary, or plasma). We suggest that both the quantity and the quality of the data used should be the main criteria, but there is no information on quality, other than the fact that a constant fractional SD of 0.1 was used by the CONSAM program (3) when the tracer data sets were fit in the compartmental model. Are we to assume that the fecal, urinary, and plasma data all had the same uncertainty associated with them? This seems unlikely given that the sample preparations were all different and that the quantity of zinc in each sample varied widely. The precision of the parameter estimates from an earlier report by Lowe et al (2) was generally good, reflecting the excellent structure and design of the model. However, in 5 of the 6 subjects, the CV for the parameter associated with urinary excretion was >60%. On the basis of these results, we estimated that the removal of the urinary data from the model would not weaken it.

A criticism of any model is that it is just that: a model. The modeling process makes gross simplifications of the way the body works and any results from it should be scrutinized for false assumptions, unjustified complexity, and unsubstantiated claims of parameter precision. In Lowe et al’s (1) discussion, there was plenty of excellent, well-argued criticism of the other methods used to calculate FZA but no criticism of the compartmental model against which these other methods were compared. Attention should have been drawn to the shortcomings of using modeling in nutritional studies so that other investigators would not be left with the impression that the results from a compartmental model are beyond contradiction.

Another weakness of Lowe et al’s study (1) was the small number of data sets used. Detailed metabolic studies are often constrained by the resources available, thus limiting the number of subjects studied, the procedures that can be undertaken, or both. Although the results obtained from the different methods reviewed was interesting, the method of comparison used was not appropriate. The FZA calculated from the compartmental model is based on an equation containing 2 of the rate constants ($k_{1,5}$ and $k_{6,5}$), which are simultaneously fitted with the other rate constants to the data set provided. There are uncertainties associated with these parameters that were not stated in Lowe et al’s (1) article, although these uncertainties were addressed in their previous study (2) in which the compartmental model was developed. In their more recent article, Lowe et al (1) used the mean and SD of the FZA calculated from the compartmental model, generated from the 6 subjects, as their reference point. Calculation of the SD of the 6 results could give a misleading picture of how good the estimate of the reference FZA is. For instance, if the uncertainties concerning the rate constants $k_{1,5}$ and $k_{6,5}$ are large for each individual subject’s data, the corresponding uncertainty concerning each calculated FZA will be large. If, however, the difference between each of the 6 calculated FZAs is, by chance, small, the SD of the mean FZA will be small. This is the drawback to having only 6 data sets and it applies equally to other methods used to calculate FZA. The conclusion that “We therefore recommend the DITR technique

with use of a spot urine sample collected ≥ 2 d after tracer administration. . .” cannot, therefore, be justified from the data provided in Lowe et al’s (1) article.

Because of the limited number of subjects in Lowe et al’s (1) study, it would have been more worthwhile to analyze each subject’s data separately and to examine the random and systematic errors associated with both the collection of that data and the calculation of the FZA. The different methods could then have been assessed genuinely within each individual. Although this type of analysis would not make clear which absorption value is the most accurate, it would enable investigators to gauge which method produces a value for FZA with the lowest associated uncertainty.

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Reply to JR Dainty et al

Dear Sir:

Dainty et al make some good points in their letter about our article (1). They suggest that the comparison of the fractional zinc absorption (FZA) data of each subject obtained by using the compartmental model with the same data obtained by using simpler measures is not the best technique for determining the accuracy of the simpler techniques. They point out that random fluctuations in the data may be propagated in the simple estimates of FZA in unpredictable ways, possibly resulting in a spurious comparison. We agree and are currently studying a theoretical data set generated from the compartmental model with a precision much greater than what could be expected in an *in vivo* tracer study of zinc metabolism; we will use this data set to determine how accurately FZA values obtained with the simple measures compare with FZA values obtained with the compartmental model. With use of this strategy, only logical deficiencies associated with each of the simple techniques relative to the compartmental model would be elucidated.

Although we agree in part with the comments of Dainty et al, we disagree with their comments on the nature and usefulness of compartmental modeling. It is true that a compartmental model of a metabolic system is a kinetic hypothesis describing how that metabolic system functions dynamically and, therefore, it is open to criticism and further testing, as is any other hypothesis. Nevertheless, because a compartmental model (the parameters of which are estimable from the data) must be consistent with all of the data to which it is applied (ie, zinc tracer and tracee measurements in plasma, urine, and feces in our study), it is a more robust description of the physiology than is a simple measure or model of a limited portion of the entire data set. Thus, the compartmental model should serve as the gold standard against which other simpler measures of the data can be compared (the problem of “noisy” data mentioned above notwithstanding). In fact, if a simple measure of the data is a good estimate of a particular physiologic parameter or combination of parameters (eg, FZA) and is also estimable in the compartmental model, such a measure could be derived within the logical context of the compartmental model.

Dainty et al suggest that any model makes “gross simplifications of the way the body works.” We agree. Nevertheless, however gross such simplifications may be in compartmental models, they are even more gross for simple measures of the data. Dainty et al mention the possibility of “false assumptions” in compartmental models, which is always a possibility, but they do not mention what these false assumptions might be in our model of zinc metabolism. They also criticize the “unjustified complexity” of our model. However, our model (2) is the simplest compartmental structure that fits all of our data. As is true with many mechanisms in nature, metabolic systems are complex and our “gross oversimplifications” (compartmental models) are often more complex than we would like. However, such complexity should not push us to retreat to gross oversimplifications and the use of simple unproven approaches for estimating various parameters (ie, FZA).

Dainty et al also refer to our “unsubstantiated claims of parameter precision.” The precision of our parameter estimates from the SAAM II computer program (SAAM Institute, Seattle) uses relative data weighting of the highest quality, and the algorithms used are well documented (3). In brief, the fractional SDs for a data array are entered as input estimates of 0.1 (relative weights) into the SAAM II program. The program then adjusts this value up or down for each data set, depending on the quality of the least-squares fit of the model to the data. The uncertainty estimates for each parameter are then scaled accordingly. We apologize for a misprint in footnote 1 to Table 2 in our original article (2), which apparently has generated concern about the precision of our estimates. The uncertainty estimates for each parameter in that table are fractional SDs, not SDs, as indicated in the footnote. Thus, the average fractional SD of the rate constant $k_{0,1}$, which describes the fractional movement of zinc tracer and tracee from the plasma to the urine per unit time, is $\approx 13\%$, not $>60\%$.

In conclusion, we agree with Dainty et al that comparison of the adequacy of simple measures of FZA from a particular data set cannot be compared easily with the estimation of FZA from the compartmental model because of the uncertain way in which the random fluctuations in the data get propagated in the

simple estimates of FZA. A more rigorous theoretical comparison of simple with compartmental modeling techniques is currently under way. Nevertheless, we believe that the comments made by Dainty et al about compartmental modeling are misguided. The more robust the hypothesis, ie, the more extensive and more different the data set explained by a model (in our case zinc tracer and tracee data in plasma, urine, and feces over 6 d after administration of oral and intravenous tracers), the more accurate a particular measure of a model (ie, FZA) is likely to be. Under such conditions, we believe it is appropriate to use a well-documented compartmental model as the gold standard for evaluating the accuracy of simple estimates of a parameter such as FZA.

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Relation between basal metabolic rate and body composition in subjects with anorexia nervosa

Dear Sir:

The cross-sectional study of Polito et al (1) examined the relation between basal metabolic rate (BMR) and anorexia nervosa. In the introduction to their article, Polito et al state that many studies showed a reduced BMR in subjects with anorexia nervosa and that “the main controversy remains whether the

decrease in BMR is due to a change in body composition or whether it represents a down-regulation of cellular metabolism.” These authors conclude from their findings that BMR is depressed in subjects with anorexia nervosa and that this is not explained by changes in body composition. This suggests that “. . . the metabolic activity of the active tissue mass may have been reduced” in subjects with anorexia nervosa.

I am not sure that the conclusions of Polito et al are justified because these authors did not adequately control for differences in body composition. Although they did control appropriately for fat-free mass by using analysis of covariance, their data (Table 1 of the article) show that the biggest difference in body composition between subjects with anorexia nervosa and control subjects is in fat mass and not fat-free mass. Fat mass was 57% lower in patients with anorexia nervosa than in control subjects (6.8 compared with 15.7 kg, respectively), whereas fat-free mass was only 16% lower (34.7 compared with 41.2 kg). It is now recognized that fat mass also makes a contribution to BMR (2) and recent studies controlled for both fat mass and fat-free mass when comparing BMR between groups (3–6).

If Polito et al had used fat mass and fat-free mass as covariates when comparing BMR, it is possible that group differences would have been eliminated, which would suggest that body composition differences were responsible for the reduced BMR values in subjects with anorexia nervosa. Such a contention is supported by the fact that when Polito et al used body weight as a covariate instead of fat-free mass they found no difference in BMR between subjects with anorexia nervosa and control subjects. In fact, if a single covariate is to be used for the data of Polito et al, it would be more appropriate to use body weight than to use fat-free mass. The rationale for using fat-free mass as a single covariate is that it is the best predictor of BMR (7). However, the data of Polito et al show that, for their subjects, body weight and not fat-free mass was the best BMR predictor ($r^2 = 0.62$ and 0.48 for body weight and fat-free mass, respectively; Figure 1 of the article).

Thus, a plausible explanation for the lower BMRs in subjects with anorexia nervosa after control for fat-free mass is their greatly reduced fat mass. To eliminate this possibility, Polito et al could reanalyze their data using analysis of covariance to control for both fat mass and fat-free mass. This would either strengthen their conclusion that reductions in BMR with anorexia nervosa are not due to body composition changes or invalidate that conclusion.

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