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Letters to the Editor

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Drs. Erenberg, Omori, Oh, and Fisher presented data on the metabolism of thyroid hormones in sheep after fetal thyroidectomy in *Pediatric Research* [3]. Their primary data consist of specific activity-time curves for thyroxine and triodothyronine which were analyzed by fitting a straight line to the final slope to yield volumes of distribution and half-lives. These two variables plus plasma concentration of the hormone are then used to compute the production rate or degradation rate of the hormone, a quantity called the "turnover rate" in the article. However, using the final linear portion of the decay curve disregards the data of the first 12–24 hr, data which imply a more complicated model than a single pool open system. There is precedence for a more complicated model for thyroxine metabolism [1, 4, 5], which appears to be at least a two-pool model with inflow into *pool 1* and loss from *pool 2*. Such a model would imply that a sum of two-exponential equation is needed to fit the data. Using a computer program we have developed [2] a sum of two-exponential equation has been fitted to the mean data given in Figure 2 of the article by Erenberg *et al.* with the results shown in Table I.

The zero time intercept of the fitted curve gives the volume of the first pool and the volume of the second pool is obtained from the variables of the fitted two-exponential equation. The total volume computed in this manner is considerably less than those given in Table II of the article by Erenberg *et al.* The half-time differs by 5 to 6% and varies in direction. The comparisons are somewhat tentative since the authors have presented only the mean data and we obtained the variables that best fitted the mean data rather than the means of the variables that best fitted each set of data. However, it is possible to show theoretically that the half-time computed from the rate constant of the second exponential of the two-exponential response of the two-pool system is lower than the true half-time for the whole system. Furthermore, the discrepancy increases as more of the total volume of the system is in *compartment 1* and as the rate of interchange between the compartments decreases. It is worth pointing out the curious fact that when excretion is from *pool 2* and measurements are made in *pool 1,* the discrepancy is under 10% over a fairly wide range of compartment sizes and exchange rates. The turnover rates, when multiplied by 100, give the percentage of the total mass of thyroxine turning over per unit time (per hour in this case). The turnover rate is related to the half-time. Finally, the degradation rates are some 20% less than given in Table II of the article by Erenberg *et al.,* since total volume was so inaccurately estimated. The degradation rate divided by total mass of thyroxine in the system is the turnover rate only for a system with single inflow and single outflow monitored at the outflow pool.

Table 1. Sum of two exponential equation fitted to mean data of article by Erenberg *et al.*

	Total volume, liters	$t_{0.5}$, days	Turnover rate, hr^{-1}	Degradation rate, μ/24 hr
Maternal	9.94	1.35	0.0213	432
Fetal	0.86	1.05	0.0274	3.9

In summary, analysis of specific activity-time curves requires careful thought as to the type of model one is going to fit to the data. It is not sufficient simply to fit a straight line to the terminal portion of curve.

References and Notes

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Drs. Dell and Ramakrishnan are quite correct when they comment "analysis of specific activity-time curves requires careful thought as to the type of model one is going to fit to the data." We and they have applied a two-compartment model to the T4 tracer data, and it is important to point out that both analysis systems indicate fetal hypothyroidism and imply minimal placental T4 transfer. The "final slope" approach which we employed entails calculation of the biological half-life and *apparent* distribution volume from the final single exponential disappearance curve. It is quite true that this method *always* leads to estimates of plasma or metabolic clearance rates which are biased to some degree, and the method can be used only if it has been shown that the bias is minimal. In comparative studies estimating metabolic clearance of T4 or T3 by "final slope" analysis of single tracer injection curves on the one hand and either whole body counting or the constant infusion method on the other, we had obtained similar estimates of clearance [4, 5]; thus, at the time our experiments were conducted, we had assumed that the bias in the "final slope" approach was minimal for iodothyronine kinetics. However, in recent computer simulation studies conducted in collaboration with Dr. Joseph DiStefano III, it has become clear that this is not the case, particularly in noneuthyroid subjects [3]. Thus, a more sophisticated approach, such as the two-exponential approach of Drs. Dell and Ramakrishnan, would be preferable to the "final slope" method in these studies of the hypothyroid fetus.

Ideally, the model-free integration method is the simplest and, in principle, most accurate method for calculating metabolic clearance rates when sufficient data is available [6].

However, as another alternative for studies in the maternal-fetal system, we have proposed an explicit model to obtain steady state maternal and fetal hormone disposal rates as well as placental transfer rates during dual tracer studies [2]. This approach requires no knowledge of actual hormone distribution patterns or distribution volumes and is available for computer application.

In summary, we agree with Drs. Dell and Ramakrishnan that there are more accurate approaches to analysis of tracer kinetic data than the "final slope" method which now has very limited application. The weighted least squares technique [1] is one of these.

We would emphasize again, however, that reanalysis of our data using this approach reduced the apparent T4 distribution volume and T4 turnover in the fetus some 20%, so that the thyroidectomized fetus is even more hypothyroid.

References and Notes

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