for $0 \leq t \leq b$ and:

$$L^{-1}\{a_{s,3}\} = k_{13}k^0\left[\frac{E_2 b}{\alpha\beta} + \frac{(E_2-\alpha)(1-e^{\alpha b})e^{-\alpha t}}{\alpha^2(\beta-\alpha)} + \frac{(E_2-\beta)(1-e^{\beta b})e^{-\beta t}}{\beta^2(\alpha-\beta)}\right] \quad \text{(Eq. 13)}$$

for $t > b$. Equation 13 coincides with Eq. 24 (1), which is valid for the model only after infusion has ceased. Equation 12 gives a very explicit form of the solution during the infusion time.

It is hoped that the corrections made in this article can contribute to the broader application and understanding of the method proposed by Benet.

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Mathematical Treatment of Linear Mammillary Models Using Inverse Laplace Transforms: A Reply

Keyphrases □ Mammillary models, linear—mathematics, inverse Laplace transforms □ Laplace transforms—inverse, in mathematical treatment of linear mammillary models □ Mathematics—inverse Laplace transforms in linear mammillary models

To the Editor:

The impetus for preparing my 1972 paper on the general treatment of linear mammillary models as used in pharmacokinetics (1) was a sense of frustration with the pages of mathematical derivation included as part of each pharmacokinetic paper that appeared in print up to that time. As I stated in the introduction (1): "This paper intends to present some very simplified general treatments which will allow workers to derive equations for any linear mammillary compartment model with any first- or zero-order input process." I believed then, as I believe now, that pharmacokinetic compartment models are useful only as a convenient means to describe and predict the time course of measurable body fluid compartments such as plasma, blood, and urine following single and multiple doses. I did not consider the possibility of input into a peripheral compartment or the general derivation for such a treatment, as was described by Vaughan and Trainor (2), since I believe this use of compartment models is inappropriate, *i.e.*, defining one compartment in the model as specifically describing an organ in the body such as the liver. Such a combination of compartment and perfusion models requires exponential terms that are not needed to fit the minimal compartment model adequately and leads to difficulties in interpreting "absorption" rate constants for such a system.

Haborak *et al.* (3) questioned the solution of two equations in my earlier paper, stating: "The presence of the factor $(1 - e^{-bs})$ destroys the polynomial character of the numerator, so neither the General Partial Fraction Theorem nor the Heaviside expansion immediately pertains." They are correct. However, the correct solution is also obtained using the one-step method that I proposed (1, 4). Apparently, the restriction concerning the polynomial character of the numerator may be relaxed when exponential functions appear in the numerator due to the inclusion of a zero-order input function. Since I am no mathematician, I shall leave the proof of this exception to others. However, I have tested the one-step method and found that it gives the correct equations for the usual multicompartment pharmacokinetic models with zero-order input into the central or peripheral compartments.

The authors of the preceding article (3) were most disturbed by the fact that I proposed the use of a single equation to describe the time course of drug in the central compartment during infusion *and* when infusion has ceased. Although I did explain, following Eq. 13 (1), that this approach was equivalent to using two independent variables, t = clock time and b = infusion time, Haborak *et al.* (3) stated that "changing constants to variables in the middle of a derivation confuses the reader . . .." I must admit that this point has led to questions by a number of readers over the years. Perhaps the preceding note and this reply will help readers to understand the appropriate use of Eqs. 13 and 24 in the 1972 paper (1).

Haborak *et al.* (3) also stated that my use of a single equation "requires very tedious calculations." This statement I do not understand; it certainly would be quicker to calculate A_1 values in Eq. 13 on any programmable calculator using a single equation with two inputs during the infusion phase than it would be using two different equations. But "calculation" is not the important functional use for Eq. 13. In 1972, I was concerned that investigators were fitting data from the postinfusion phase separately from the infusion phase. This procedure is inappropriate, as I stated previously (1). In 1972, many of the computer programs used to fit pharmacokinetic data, particularly the BMD series (5), only allowed the investigator to fit one function at a time. However, I stated then (1) that: "All the least-squares nonlinear fitting programs usually utilized in pharmacokinetic treatments have the ability to fit data to Eq. 13. . . ."

In conclusion, the previous article (3) points out the detailed solution for the Laplace derivation when an exponential operator term appears in the numerator of the

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Laplace transform. Hopefully, that paper and this response will allow the uninitiated reader to understand better the use of such functions. However, once the reader becomes initiated (*i.e.*, not confused), I suggest he or she define b as the time of infusion rather than the time when infusion ends and use the anti-Laplace techniques and equations presented in my 1972 publication. They really are easier to use.

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Time-Dependent Kinetics VI: Direct Relationship between Equations for Drug Levels during Induction and Those Involving Constant Clearance

Keyphrases □ Pharmacokinetics—time dependent, equations for drug levels during induction and during constant clearance □ Models, pharmacokinetic—equations for drug levels during induction and during constant clearance

To the Editor:

In a previous report (1), equations were derived to describe the time course of drug levels during enzyme induction under various drug input conditions: single-dose intravenous (Case I) and oral (Case II) administration, constant rate intravenous infusion (Case III), and multiple-dose intravenous (Case IV) and oral (Case V) administration. These equations were based on the following assumptions:

1. Drug distribution is instantaneous (one compartment of volume V).
2. Drug is excreted unchanged by first-order processes.
3. Metabolism occurs by several first-order pathways, with one being controlled by a single inducible enzyme.
4. Metabolic clearance (pre- and postinduction) approaches intrinsic clearance.
5. Total body drug clearance increases during induction from a preinduction value $Q(t \leq \lambda)$ to a maximum Q' according to (2):

$$Q(t) = Q' - (Q' - Q)\exp[-k'(t - \lambda)] \qquad \text{(Eq. 1)}$$

where k' represents the first-order degradation rate constant of the induced enzyme, $k' < 0.1\ Q'/V$, and λ is the time at which induction begins.

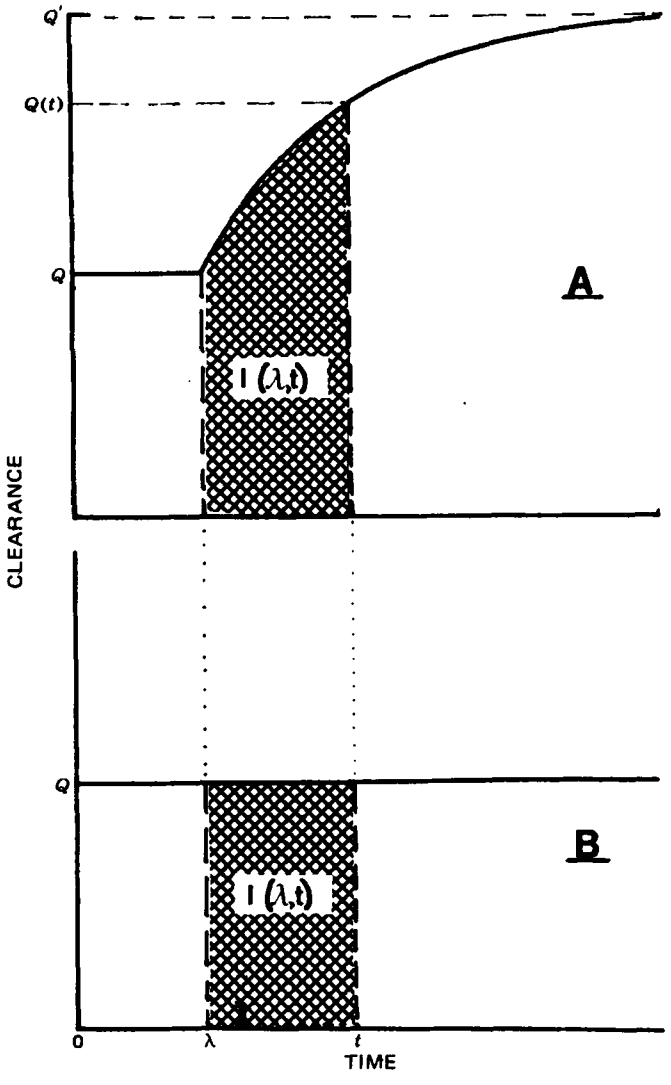

Figure 1—*Exponent* I(λ, t) *in time-dependent kinetics (A) and in linear kinetics (B). Whereas in linear kinetics (constant clearance) the area term* I(λ, t) *increases proportionately with time, in time-dependent kinetics the increase in area is more than proportional.*

To date, equations based on an exponentially increasing clearance have been validated only to the extent that the time course of blood levels that they predict is compatible with some experimental observations (3–7). In this report, a mathematical proof is presented to show that these equations are consistent with the corresponding equations of the classical one-compartment model with constant clearance. In fact, the latter represent a particular case of the former.

Table I presents solutions for Cases I–V with corresponding solutions for the one compartment with constant clearance.

Figure 1 is a plot of $Q(t)$ *versus* time. The term $I(\lambda, t)$ in every equation involving a time-dependent clearance (Table I) is defined as:

$$I(\lambda, t) = \int_{\lambda}^{t} Q(u)\,du \qquad \text{(Eq. 2)}$$

and, therefore, represents the area under the $Q(t)$ *versus*

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