Table I—Dissolution Rates[a] of Cholesterol Monohydrate Pellet (J/A), Solubilities (C_s), and Diffusion Coefficients (D) Independently Determined in the Solvent Media at 37°

0.1 *M* Phosphate, pH 7.4						
Cholate, %	Lecithin, %	Benzalkonium Chloride, %	$(J/A)10^4$, mg. cm.$^{-2}$ sec.$^{-1}$	C_s, mg. cm.$^{-3}$	$D \times 10^6$, cm.^{2} sec.$^{-1}$	$R \times 10^{-3}$, sec. cm.$^{-1}$
2.0	—	—	0.67	0.53	2.17	7.91
2.0	—	0.5	4.82	0.63	1.92	1.31
2.0	1.0	—	0.16	1.05	1.49	65.63
2.0	1.0	0.5	4.82	1.37	1.50	2.84
5.0	—	—	1.95	1.34	1.90	6.87
5.0	—	1.25	8.95	1.71	1.54	1.91
5.0	2.5	—	0.56	3.0	1.30	53.57
5.0	2.5	1.25	8.33	3.27	1.10	3.93
Benzoic acid in 0.01 *N* HCl			131.0	4.70	14.0	3.59

[a] R was calculated from $J/A = C_s/R$, where $R = h/D + 1/p$ with h = Nernst diffusion layer thickness and p = effective interfacial permeability coefficient.

nearly that found with benzoic acid dissolution. Similar effects with benzalkonium chloride were also found in 2 and 5% cholate. Other dissolution studies in 2% cholate–1% lecithin showed that 0.5% cetylpyridinium chloride may have the same effect as benzalkonium chloride, giving $R = 4.85 \times 10^3$ sec. cm.$^{-1}$; 0.5% cetrimonium bromide was around 80% as effective as benzalkonium chloride, giving $R = 10.3 \times 10^3$ sec. cm.$^{-1}$. Experiments with human cholesterol gallstones were conducted by reported methods (2) in 2% cholate–1% lecithin solutions, with or without 0.5% benzalkonium chloride. Similar results as those shown in Table I for cholesterol monohydrate pellets were obtained: $R = 1.57 \times 10^3$ sec. cm.$^{-1}$ and $R = 61.76 \times 10^3$ sec. cm.$^{-1}$ with and without benzalkonium chloride, respectively.

The clinical implications of these findings with the quaternary ammonium compounds may be important in the medical treatment of the gallstone disease. Recent clinical studies of Danzinger *et al.* (3) showed that oral administration of chenodeoxycholic acid to patients with gallstones can lead to the undersaturation of the bile with respect to cholesterol and the dissolution of the stones. They found that, in six of the seven patients studied, gallstones progressively diminished in size during the 14–30 months of chenodeoxycholic acid treatment. In a different kind of study by Admirand[1] involving the dissolution of cholesterol gallstones retained in the common bile duct postoperatively *via* T-tube perfusion of 5% cholate, small stones of millimeter diameter were dissolved in 3–14 days while larger stones did not appear to diminish significantly. These studies support the idea that increasing the *in situ* gallstone dissolution rate should yield material patient benefits through reduced medical treatment times. The results and methodology reported with benzalkonium chloride and other quaternary ammonium compounds may prove valuable in finding or designing safe and efficacious agents or therapeutic regimens for the medical treatment of the gallstone disease.

(1) W. I. Higuchi, S. Prakongpan, V. Surpuriya, and F. Young, *Science*, **178**, 633(1972).

(2) W. I. Higuchi, S. Prakongpan, and F. Young, *J. Pharm. Sci.*, **62**, 945(1973).

[1] W. H. Admirand, University of California Medical Center, San Franciso, Calif., personal communication.

(3) R. G. Danzinger, A. F. Hofmann, L. J. Schoenfield, and J. L. Thistle, *N. Engl. J. Med.*, **286**, 1(1972).

WILLIAM I. HIGUCHI
SOMPOL PRAKONGPAN
FUDAH YOUNG▲
College of Pharmacy
University of Michigan
Ann Arbor, MI 48104

Received March 5, 1973.
Accepted for publication April 20, 1973.
▲ To whom inquiries should be directed.

Obtaining Preliminary Estimates to Fit Two-Term Exponential Model to Blood Concentration Data

Keyphrases ☐ Absorption and elimination rate constants, preliminary estimates—obtained using exponential function curve fitting ☐ Blood concentration data—preliminary estimates for two-term exponential model, equations ☐ Rate constants, absorption and elimination—preliminary estimates for two-term exponential model, method, equations

Sir:

For a two-term exponential model, Wagner (1) discussed a graphical method of obtaining preliminary estimates of the elimination and absorption rate constants. In a later paper, Wagner and Metzler (2) concluded, by illustrating two examples, that graphical estimates (obtained by conventional feathering techniques) of the absorption rate constant and the elimination rate constant overestimate and underestimate the corresponding rate constants obtained by the least-squares solution. Wagner (1) noted that, if the starting values for the computer program are not close to the least-squares estimates, some computer programs may not necessarily converge at the global minimum because the error sum of squares may contain two minima. This communication presents another method of ob-

Table I—Lowest Serum Levels of Tetracycline Hydrochloride[a] Activity Observed in a Panel of Eight Subjects Administered 250 mg. after Specified Breakfast

Time, i	Serum Concentration of Tetracycline Hydrochloride, C_i	S_{1i}	S_{2i}
0	0.7000	0.7000	0.7000
1	1.2000	1.9000	2.6000
2	1.4000	3.3000	5.9000
3	1.4000	4.7000	10.6000
4	1.2381[b]	5.9381	16.5381
5	1.1000	7.0381	23.5762
6	0.9650[b]	8.0031	31.5794
7	0.8000	8.8031	40.3825
8	0.7312[b]	9.5343	49.9168
9	0.6000	10.1343	60.0512
10	0.5456	10.6800	70.7311
11	0.5000	11.1800	81.9111
12	0.4057[b]	11.5857	93.4968
13	0.3497[b]	11.9354	105.4322
14	0.3013[b]	12.2385	117.6707
15	0.3000	12.5385	130.2091

[a] Panmycin. [b] Indicates that these values are estimated using Eq. 7 of *Reference 1*.

taining preliminary estimates of the rate constants for a two-term exponential model. These estimates may then be used as initial starting values in a digital computer program, providing more assurance that the computer program will converge at the global minimum within a few iteration steps.

Let us suppose that we are able to observe C_t, the serum concentration of an investigational drug at time t. Furthermore, let the two-term exponential model be of the form:

$$E(C_t) = \beta_1 e^{\alpha_1 t} + \beta_2 e^{\alpha_2 t} \qquad t = 0, 1, \ldots, n \qquad \text{(Eq. 1)}$$

where E is the mathematical expectation, and α's and β's are the population parameters of the model for the drug under investigation. In clinical practice, a subject is selected at random and the values of C_t are assayed at equal intervals of time. Thus, the two-term exponential equation in the sample situation can be written as:

$$C_t = b_1 e^{\alpha_1 t} + b_2 e^{\alpha_2 t} = b_1 d_1^t + b_2 d_2^t \qquad t = 0, 1, \ldots, n \qquad \text{(Eq. 2)}$$

Because of the algebraic structure of Eq. 2, it is possible to rewrite the model in the form of a difference equation:

$$(C_{t+2} - C_{t+1}) - (C_{t+1} - C_t) = r_2 C_{t+2} - r_1 C_{t+1} \qquad \text{(Eq. 3)}$$

where:

$$d_1 + d_2 = (2 - r_1)/(1 - r_2) \qquad \text{(Eq. 4a)}$$

$$d_1 d_2 = 1/(1 - r_2) \qquad \text{(Eq. 4b)}$$

Summing Eq. 3 over the values of i from 0 to $i - 2$, we have:

$$C_i - C_{i-1} = (r_2 - r_1)S_{1i} + r_1 C_i + f \qquad \text{(Eq. 5)}$$

where $S_{1i} = \Sigma_0^i C_k$ and $f = C_0(r_1 - r_2) - r_2 C_1$.

Again, summing Eq. 5 over the values of i from 1 to i, we have:

$$C_i = (r_2 - r_1)S_{2i} + r_1 S_{1i} + if + g \qquad \text{(Eq. 6)}$$

where $S_{2i} = \Sigma_0^i S_{1k}$ and $g = C_0(1 - r_2)$.

Equation 6 is known as the internal regression (3) of Eq. 2; the values of constants, namely, $(r_2 - r_1)$, r_1, f, and g, can be obtained[1] by regressing C_i on S_{2i}, S_{1i}, and i. Having obtained these values from the data, we can then estimate d_1 and d_2 from the following equation:

$$(\hat{d_1}, \hat{d_2}) = \{1 - r_1/2 \pm \sqrt{(r_2 - r_1) + r_1^2/4}\}/(1 - r_2) \qquad \text{(Eq. 7)}$$

Theoretically, it is possible that the roots may be complex. However, if this situation does arise, then Eq. 2 can be mathematically expressed as sine, cosine functions, indicating that the two-term exponential model may not be appropriate. To illustrate the methodology, certain values of serum levels of tetracycline hydrochloride activity (Table I) from Eq. 7 (1) were interpolated to make the data equally spaced.

Using the linear regression set up by considering S_{1i}, S_{2i}, and i as independent variables and C_i as a dependent variable, we find the following regression coefficients (Eq. 6): $\hat{r}_2 - \hat{r}_1 = -0.1733$, $\hat{r}_1 = -1.2486$, $\hat{f} = 2.4522$, and $\hat{g} = 1.6671$. Now, using Eq. 7 or 4, we find $(\hat{d}_1, \hat{d}_2) = (0.862, 0.479)$ or:

$$\hat{a}_1 = \ln \hat{d}_1 = -0.14761 \qquad \text{(Eq. 8a)}$$

$$\hat{a}_2 = \ln \hat{d}_2 = -0.73697 \qquad \text{(Eq. 8b)}$$

Having obtained $\hat{a}_1$ and $\hat{a}_2$, we can obtain $\hat{b}_1$ and $\hat{b}_2$ by regressing C_t on $\exp(\hat{a}_1 t)$ and $\exp(\hat{a}_2 t)$:

$$\hat{b}_1 = 2.75726 \qquad \text{(Eq. 9a)}$$

$$\hat{b}_2 = -3.54831 \qquad \text{(Eq. 9b)}$$

Thus, the two-term exponential model (2) can be written as:

$$C_t = 2.75726e^{-0.14761t} - 3.54831e^{-0.73697t} \qquad \text{(Eq. 10)}$$

indicating that the rate constants $\hat{a}_1$ and $\hat{a}_2$ are very near to the least-squares estimates of -0.149 and -0.716.

The method does provide good starting values for a computer program. Convergence is achieved within one or two steps of iteration, indicating that the method of obtaining the estimates is nearly 100% efficient with respect to the least-squares method. The analytical comparison of efficiencies of the estimates with the standard least-squares estimate is currently under investigation.

(1) J. G. Wagner, *Clin. Pharmacol. Ther.*, **8**, 201(1967).
(2) J. G. Wagner and C. M. Metzler, *J. Pharm. Sci.*, **56**, 658 (1967).
(3) H. O. Hartley, *Biometrika*, **35**, 32(1948).

B. K. Shah
Research Center
Rockland State Hospital
Orangeburg, NY 10962

Received November 3, 1972.
Accepted for publication March 28, 1973.
Supported in part by Grant MH 23970 from the National Institute of Mental Health and by General Research Support Grant S01 RR05651 from the Department of Health, Education, and Welfare.
The author is grateful to Professor John Wagner for his useful comments.

[1] To obtain approximation to the parameters, we may consider S_{1i} and S_{2i} as independent variables in the linear regression equation (6).