tological changes in this study were shorter than those reported by Strakosch (11). These differences may be ascribed to the use of rat rather than human skin or different base formulations. Strakosch also found that the onset of keratolysis was markedly dependent on the base used, the onset being two to three times more rapid for salicylic acid in the oxycholesterol–petrolatum base than in the petrolatum base. Since higher blood salicylic acid levels were observed from the topical application of salicylic acid in a hydrophilic ointment base compared to a petrolatum base (1), keratolysis apparently depends on the absorption rate of the salicylic acid from the particular formulation.

Following the initial keratolytic process in which morphological changes were observed in the stratum spinosum, stratum granulosum, and stratum corneum, further repeated applications of salicylic acid gave rise to the formation of a broad stratum corneum. The process by which this broad stratum corneum formed was not clearly evident but may have resulted from diminished fluxes after prolonged daily (Fig. 3) or weekly (Fig. 2) treatments.

Since the salicylic acid being applied still exerts its surface keratolytic effect, reduced absorption *in vivo* may be due not only to the thicker horny layer but also to the process of desquamation. The results of this study, using an *in vitro* diffusion apparatus, suggest that the thicker horny layer does offer greater resistance to the penetration of salicylic acid.

Recent work by Davies and Marks (12) did not substantiate the increased epidermopoiesis resulting from the application of salicylic acid to human skin as described by Strakosch (11). Davies and Marks did observe differences in the horny layer structure and thickness in treated and untreated samples of skin. As stated by Davies and Marks (12), it is possible that their experimental conditions were not sufficiently severe or of a sufficient duration for increased epidermopoiesis to be observed.

Although the present histological and physiochemical results are consistent with a dynamic equilibrium between keratolysis and regeneration of the epidermis, the precise cytological changes in the epidermis following salicylic acid therapy have yet to be fully documented. The changes resulting from the present experimental conditions are being examined using transmission electron microscopy.

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ESTRIP, a BASIC Computer Program for Obtaining Initial Polyexponential Parameter Estimates

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Abstract □ A new BASIC exponential stripping program, ESTRIP, allows the relatively rapid calculation of initial polyexponential parameter estimates, as does the previously published FORTRAN IV program, CSTRIP. The potential advantages of the new program are that it can be run on microcomputers and minicomputers with BASIC capability and a relatively small core and that it can be easily modified by the user.

Keyphrases □ Computer programs—ESTRIP for calculation of initial polyexponential parameter estimates □ Pharmacokinetic models—ESTRIP computer program for calculation of initial polyexponential parameter estimates □ Models, pharmacokinetic—ESTRIP computer program for calculation of initial polyexponential parameter estimates

The mathematical solutions of classical linear pharmacokinetic models are given by the sums of exponential terms. The generalized equation for these models can be written as:

$$C = \sum_{i=1}^{u} a_i e^{-b_i t} \qquad \text{(Eq. 1)}$$

where C is the concentration of drug at time t, u is the number of exponential terms, and a_i and b_i are the parameters to be determined.

Computer programs for the estimation of these polyexponential parameters (1, 2) generally require sophisticated computers utilizing BMD, BMDP, SAS, or other expensive software packages and are usually available on a time-sharing, batch-job basis. One exception is the CSTRIP program (3), which can be used to obtain preliminary polyexponential parameter estimates *via* an automated stripping (feathering, peeling-off, or back-projection) technique; this program requires the use of FORTRAN IV.

The purposes of this paper are to describe a new exponential stripping computer program[1] and to illustrate its use. The potential advantages of the new program are that

[1] A complete photocopy of the program listing will be supplied upon request. The program is also available, for a fee, on paper tape or a Scotch DC300A Data Cartridge.

0022-3549/78/1200-1687$01.00/0

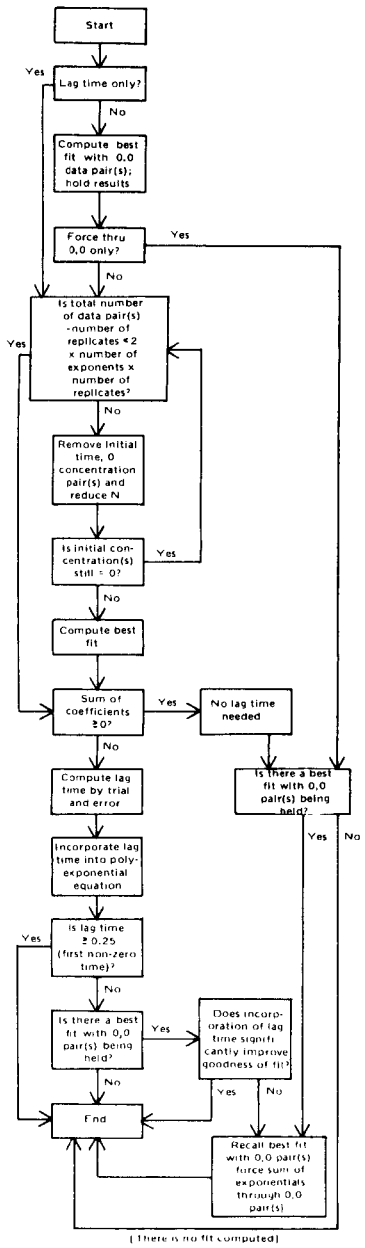

Figure 1—*Flowsheet for LGTME subroutine.*

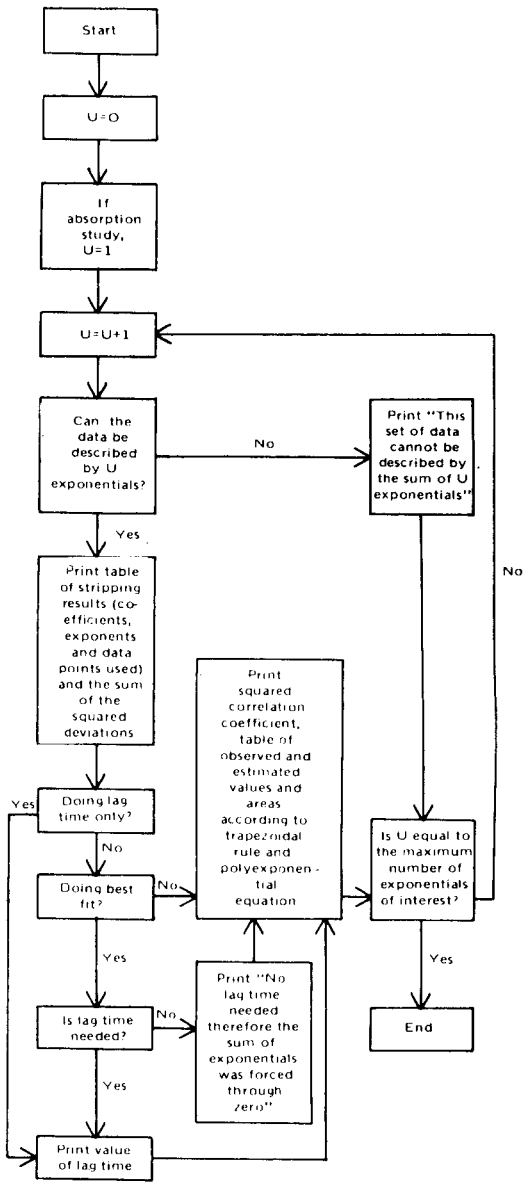

Figure 2—*Schematic diagram of ESTRIP output.*

it can be run on minicomputers and microcomputers with BASIC capability and a relatively small core (16 K or less) and that it can be easily modified by the user[2].

DISCUSSION

Computer Program—ESTRIP, a BASIC computer program for obtaining initial polyexponential parameter estimates, is based on a computer adaptation of the residual, back-projection technique. ESTRIP is composed of eight major subroutines; the most important will be discussed briefly and compared to those with similar functions in CSTRIP (3).

EXP STRIP[3]—This subroutine strips curves described by from one to five exponentials. It differs from the subroutines in CSTRIP with a similar function (3) on two observable points. To conserve core, this subroutine was written to strip one, two, three, four, *or* five exponentials rather than utilizing a separate stripping subroutine to estimate the parameters of each of the five possible exponential equations. In addition, the minimum number of points for a computer calculation of a_i and b_i is fixed at two rather than being dependent on the number of distinct time values and the number of exponential terms, with a minimum value of two.

As in CSTRIP, the value F (the sum of squares of the deviations) is used to evaluate the goodness of fit of the estimates:

$$F = \sum_{i=1}^{n} (C_i - \hat{C}_i)^2 \qquad \text{(Eq. 2)}$$

where $\hat{C}_i$ is the estimated drug concentration and n is the total number of data points.

The set of parameters obtained with EXP STRIP that has the minimum F value is chosen as the best estimate. As with CSTRIP, exponential terms describing intravenous or postabsorption (or postinfusion) data cannot have negative coefficients and, with all data, the value of b_{i-1} is required to be $\geq 1.33\ b_i$ and exponents b_i cannot assume values ≤ 0. An additional constraint in ESTRIP is that a_1 is required to be <0 in the absorption studies.

LEAST SQR—This subroutine, nested within EXP STRIP, calculates the appropriate residual regression lines using standard least-squares linear regression techniques.

[2] Finnigan BASIC was used in writing this program. The specific data system used was the Finnigan 6110, which is intended primarily for the operation of the Finnigan 3300 gas chromatograph–mass spectrometer but can be used in a non-gas chromatograph–mass spectrometer BASIC mode. The 6110 includes a Computer Automations, Inc. naked minicomputer with 16 kilobytes of random access memory.

[3] Names of subroutines are not used in BASIC; they are given in this paper for clarification purposes.

Table I—ESTRIP Output Parameters

Parameter	Comment
Subscript 1, 2, *etc.*	Subscripts of terms in polyexponential equation
A_1, A_2, *etc.*	Coefficients of exponential terms of polyexponential equation
B_1, B_2, *etc.*	Exponents of polyexponential equation
Data points used	Number of data pairs used in calculation of particular subscripted coefficient and exponent (counting backward beginning with last data)
F	Sum of squared deviations between observed data and data predicted by use of polyexponential equation
r^2	Squared correlation coefficient
Number	Data point number
Time	Abscissa values
C(obs)	Observed ordinate values
C(est)	Ordinate values predicted by use of polyexponential equation
Percent deviation	Percent deviation of observed from predicted ordinate values
Area using trapezoidal rule	$AUC_{0-t} = \sum_{i=0}^{n-1} \frac{t_{i+1} - t_i}{2} (C_i + C_{i+1})$
Area using polyexponential equation	$AUC_{0-\infty} = \sum_{i=1}^{U} A_i/B_i$

Table II—Tetracycline Data

Hours	Serum Concentration of Tetracycline Hydrochloride, μg/ml
0	0
1	0.7
2	1.2
3	1.4
4	1.4
6	1.1
8	0.8
10	0.6
12	0.5
16	0.3

SSQR DEV—This subroutine, also nested within EXP STRIP, is used to select the best fit of the sets of calculated estimates. If the constraints placed on the polyexponential parameter estimates are met in a particular set of estimates and if the F of this set is less than that of a previous set being held, the previous set is replaced. A modification of this subroutine is also used, as another nested subroutine within EXP STRIP, to determine the value of the sign placed on the coefficient a_i.

RSQR—This subroutine calculates r^2:

$$r^2 = \left[\sum_{i=1}^{n} C_i^2 - \frac{\left(\sum_{i=1}^{n} C_i\right)^2}{n} - \sum_{i=1}^{n} (C_i - \hat{C}_i)^2 \right] \Bigg/ \left[\sum_{i=1}^{n} C_i^2 - \frac{\left(\sum_{i=1}^{n} C_i\right)^2}{n} \right] \quad \text{(Eq. 3)}$$

which, with F, is used to evaluate the goodness of fit of the estimates.

LGTME—This subroutine determines whether a lag time is needed to describe the data from absorption studies. A flowsheet for the LGTME algorithm is given in Fig. 1. The lag time, t_1, is determined by a trial-and-error solution of:

$$\sum_{i=1}^{u} a_i e^{-b_i t_1} = 0 \quad \text{(Eq. 4)}$$

Use of ESTRIP Program—*Input of Time–Drug Concentration Data*—Data statements are inserted between lines 2985 and 9999 in the program before the Run command is initiated. The first Data statement contains the total number of data points and is followed by the time–drug concentration data. The following restrictions apply to the input of data to both ESTRIP and CSTRIP:

1. Abscissa (time) values must be ascendingly ordered.

```
MAXIMUM NUMBER OF EXPONENTS INTERESTED IN = ?5

IV OF POST-ABSOPPTION STUDIES = 1;
ABSORPTION STUDIES; AS DATA IS = 2; FORCE THRU 0,0 = 3;
                    BEST FIT = 4; LAG TIME = 5;?4

NO. OF REPLICATIONS = ?1

              THE NO. OF EXPONENTIALS =  2
  SUMMARY OF EXP. STRIPPING; REPORTED FROM LAST TO FIRST;

SUBSCRIPT      COEFF. (A)        EXP. (B)      DATA PTS. USED
    1          2.13352          0.128894            6
    2         -2.13351          1.03423             3

                    F =  2.6531E-02

              THE LAG TIME =  0.618479

              R SQUARE ( 2  ) =  0.979416

NO.          TIME          C(OBS)          C(EST)          % DEV
 1             1             0.7          0.682992        -13.8584
 2             2             1.2          1.27671          6.39227
 3             3             1.4          1.38774         -0.875694
 4             4             1.4          1.31428         -6.12309
 5             6             1.1          1.05763         -3.90616
 6             8             0.8          0.822865         2.75809
 7            10             0.6          0.635919         5.98652
 8            12             0.5          0.491496        -1.70088
 9            16             0.3          0.293589        -2.16364

AREA USING TRAPEZOIDAL RULE =  12.15
AREA USING POLYEXPONENTIAL EQUATION =  14.4896


              THE NO. OF EXPONENTIALS =  3
  SUMMARY OF EXP. STRIPPING; REPORTED FROM LAST TO FIRST;

SUBSCRIPT      COEFF. (A)        EXP. (B)      DATA PTS. USED
    1          1.84719          0.117265            3
    2          0.969024         0.462893            3
    3         -2.81621          0.896823            3

                    F =  2.69583E-02

              THE LAG TIME =  0.588749

              R SQUARE ( 3  ) =  0.979084

NO.          TIME          C(OBS)          C(EST)          % DEV
 1             1             0.7          0.613722        -12.3254
 2             2             1.2          1.27535          6.27897
 3             3             1.4          1.38565         -1.02517
 4             4             1.4          1.30583         -6.72642
 5             6             1.1          1.03651         -5.7718
 6             8             0.8          0.802304         0.288017
 7            10             0.6          0.62448          4.08607
 8            12             0.5          0.489403        -2.11942
 9            16             0.3          0.303919         1.30634

AREA USING TRAPEZOIDAL RULE =  12.15
AREA USING POLYEXPONENTIAL EQUATION =  14.7855


THIS SET CAN'T BE DESCRIBED BY THE SUM OF 4  EXPONENTIALS!


THIS SET CAN'T BE DESCRIBED BY THE SUM OF 5  EXPONENTIALS!
```

Figure 3—*ESTRIP analysis of tetracycline concentration and time data.*

Table III—Haloperidol Data

Hours	Plasma Concentration of Haloperidol, ng/ml
0	0
0.167	2.99
0.333	4.82
0.667	2.86
1	2.23
1.5	1.65
2	1.33
3	1.05
4	0.945
6	0.679
8	0.619
12	0.462
24	0.336
48	0.178
72	0.084

MAXIMUM NUMBER OF EXPONENTS INTERESTED IN = ? 5

IV OR POST-ABSORPTION STUDIES = 1;
ABSORPTION STUDIES: AS DATA IS = 2 FORCE THRU 0,0 = 3;
BEST FIT = 4; LAG TIME = 5; ? 4

NO. OF REPLICATIONS = ? 1

THE NO. OF EXPONENTIALS = 2
SUMMARY OF EXP. STRIPPING; REPORTED FROM LAST TO FIRST:

SUBSCRIPT	COEFF. (A)	EXP. (B)	DATA PTS. USED
1	1.52907	4.52019E-02	13
2	- 1.52907	0.226037	2

F = 45.3066

NO LAG TIME WAS NEEDED SO DATA WAS FORCED THRU 0,0 !

R SQUARE (2) = -0.760874

NO.	TIME	C(OBS)	C(EST)	% DEV
1	0	0	0	. . . . .
2	0.167	2.99	4.51448E-02	-98.4901
3	0.333	4.82	8.80252E-02	-98.1738
4	0.667	2.86	0.168583	-94.1055
5	1	2.23	0.241771	-89.1583
6	1.5	1.65	0.339457	-79.4269
7	2	1.33	0.423943	-68.1246
8	3	1.05	0.559047	-46.7574
9	4	0.945	0.657056	-30.4702
10	6	0.679	0.77191	13.6834
11	8	0.619	0.81441	31.5686
12	12	0.462	0.787416	70.4364
13	24	0.336	0.510019	51.7914
14	48	0.178	0.17461	-1.90455
15	72	8.4E-02	5.902E-02	-29.7381

AREA USING TRAPEZOIDAL RULE = 26.1144
AREA USING POLYEXPONENTIAL EQUATION = 27.0629

THE NO. OF EXPONENTIALS = 3
SUMMARY OF EXP. STRIPPING; REPORTED FROM LAST TO FIRST:

SUBSCRIPT	COEFF. (A)	EXP. (B)	DATA PTS. USED
1	0.965666	3.55743E-02	9
2	3.68443	1.14207	2
3	-4.65009	8.9605	3

F = 3.40128

THE LAG TIME = 8.465E-02

R SQUARE (3) = 0.85697

NO.	TIME	C(OBS)	C(EST)	% DEV
1	0.167	2.99	2.09326	-29.9914
2	0.333	4.82	3.22935	-33.0009
3	0.667	2.86	2.81532	-1.56224
4	1	2.23	2.22873	-5.71456E-02
5	1.5	1.65	1.64998	-9.10325E-04
6	2	1.33	1.31545	-1.09362
7	3	1.05	1.00247	-4.52651
8	4	0.945	0.882218	-6.64358
9	6	0.679	0.786703	15.862
10	8	0.619	0.729117	17.7895
11	12	0.462	0.632035	36.8041
12	24	0.336	0.412422	22.7446
13	48	0.178	0.17561	-1.34293
14	72	8.4E-02	7.47748E-02	-10.9824

AREA USING TRAPEZOIDAL RULE = 25.8648
AREA USING POLYEXPONENTIAL EQUATION = 29.8522

THE NO. OF EXPONENTIALS = 4
SUMMARY OF EXP. STRIPPING; REPORTED FROM LAST TO FIRST:

SUBSCRIPT	COEFF. (A)	EXP. (B)	DATA PTS. USED.
1	0.711191	2.96516E-02	5
2	1.8277	0.515867	4
3	4.3739	3.13509	3
4	-6.91242	29.9048	2

F = 2.44106E-02

THE LAG TIME = 0.14532

R SQUARE (4) = 0.998973

NO.	TIME	C(OBS)	C(EST)	% DEV
1	0.167	2.99	2.99	-7.97387E-06
2	0.333	4.82	4.76951	-1.04742
3	0.667	2.86	2.949	3.11186
4	1	2.23	2.16948	-2.71401
5	1.5	1.65	1.65443	0.268582
6	2	1.33	1.38826	4.38075
7	3	1.05	1.07317	2.2062
8	4	0.945	0.884614	-6.39003
9	6	0.679	0.687023	1.18159
10	8	0.619	0.595207	-3.84384
11	12	0.462	0.504448	9.18782
12	24	0.336	0.350596	4.34399
13	48	0.178	0.172082	-3.32473
14	72	8.4E-02	8.44645E-02	0.553011

AREA USING TRAPEZOIDAL RULE = 25.8648
AREA USING POLYEXPONENTIAL EQUATION = 28.6918

THE NO. OF EXPONENTIALS = 5
SUMMARY OF EXP. STRIPPING; REPORTED FROM LAST TO FIRST:

SUBSCRIPT	COEFF (A)	EXP. (B)	DATA PTS. USED
1	0.795918	3.12903E-02	2
2	-0.182529	6.23796E-02	2
3	1.15287	0.315505	3
4	4.96586	2.18112	5
5	-6.73225	21.3679	2

F = 8.38743E-02

THE LAG TIME = 0.13496

R SQUARE (5) = 0.996473

NO.	TIME	C(OBS)	C(EST)	% DEV
1	0.167	2.99	2.99	-5.58171E-05
2	0.333	4.82	4.82	0
3	0.667	2.86	3.13689	9.6814
4	1	2.23	2.23187	8.38955E-02
5	1.5	1.65	1.59736	-3.19011
6	2	1.33	1.31338	-1.24995
7	3	1.05	1.05149	0.142279
8	4	0.945	0.903468	-4.39496
9	6	0.679	0.717077	5.60776
10	8	0.619	0.606936	-1.9489
11	12	0.462	0.489291	5.90704
12	24	0.336	0.336619	0.184242
13	48	0.178	0.168783	-5.1782
14	72	8.4E-02	8.19373E-02	-2.45562

AREA USING TRAPEZOIDAL RULE = 25.8648
AREA USING POLYEXPONENTIAL EQUATION = 28.1262

Figure 4—*ESTRIP analysis of haloperidol concentration and time data (composer reproduction of teletype output).*

2. Data collected during an intravenous infusion cannot be analyzed, although postinfusion values may be analyzed.
3. Outliers should not be included in data sets.
4. Replicate abscissa and/or ordinate values are permitted.

Additionally, when replicate abscissa values are used in ESTRIP, the numerical value is entered only once in the Data statement, and it is followed by the corresponding ordinate values. All of these abscissa values must be associated with the same number of ordinate values. Any other data are entered as the abscissa–ordinate pairs.

Input of Data during Operation of ESTRIP—When Run is initiated, three questions are asked of the user. The first question is "Maximum Number of Exponents Interested In = ?" The answer can be from one through five. The second question gives the user the option of running the data with the constraints related to intravenous (postinjection or postinfusion) or postabsorption studies (answer = 1) or with the constraints related to absorption studies (answer = 2–5).

When doing absorption studies, the user can select to answer the second question with the number two (2, As Data Is). This option is useful in estimating the elimination half-life, *etc.*, of a drug in a patient who has been on the medication prior to determination of the blood drug levels since neither estimating a lag time nor forcing the sum of the exponentials through 0,0 is feasible in this type of patient with ESTRIP. If the user selects to answer this question with the number three, four, or five (3, Force Thru 0,0 only; 4, Best Fit; or 5, Lag Time only), the LGTME algorithm (Fig. 1) is used to arrive at the solution.

An additional restriction placed on the input of time–drug concentration data is related to the numerical answer given to this second question. If the answer is three or four, the initial time–drug concentration value(s) of 0 must be included in the Data statements or the program will give an error message after Run is initiated. To conserve core space, a subroutine to add the 0,0 data pair(s) is not included in ESTRIP. A subroutine to remove the initial time–0 concentration(s) data is included in the LGTME algorithm, because it is essential to the function of the algorithm.

The third and final question asked the user is "No. of Replications = ?" After this question is answered, the program runs to completion.

Data Output—The ESTRIP output format (Fig. 2) is dependent on the type of data being analyzed and the answer of the user to the second question of the program. The output parameters are defined in Table I.

Examples—Forty sets of data, some simulated and the rest from the literature, were used to evaluate the capabilities of ESTRIP. Two rep-

Table IV—Comparison of Automated and Graphical Curve Stripping of Haloperidol Concentration and Time Data[a]

Parameter	Value of Parameter Estimate			
		ESTRIP[c]		
	Graphical[b]	As Data Is and Force Thru 0,0[e]	Best Fit	AUTOAN[d]
A_1	0.661	0.661	0.711	0.671
B_1	0.0283	0.0283	0.0297	0.0284
A_2	1.341	1.20	1.83	1.347
B_2	0.355	0.338	0.516	0.369
A_3	5.525	6.60	4.37	20.57
B_3	2.147	2.21	3.14	2.97
A_4	−7.527	−8.47	−6.91	−22.80
B_4	5.94	5.52	29.9	4.22
Lag time (t_1)	0	0	0.145	0
Sum of squared deviations	1.73[f]	1.64	0.0244	0.977[f]
Squared correlation coefficient	0.932[f]	0.936	0.999	0.962[f]

[a] Data fitted to a quadriexponential equation of the form: $C = \sum_{i=1}^{4} A_i e^{-Bi(t-t1)}$. [b] From Wagner (5); data pairs grouped differently than with CSTRIP. [c] All ESTRIP estimates were rounded to three significant digits after calculation. [d] From Wagner (5): AUTOAN has incorporated in it nonlinear least-square analysis. No estimate of a lag time was made, and the data were not forced through 0,0. [e] Both options produced the same fit, because only two data pairs are used in the calculation of A_4 and B_4, one of which is the 0,0 pair. [f] Other parameters in these columns are as reported by Wagner (5). These estimates were calculated from the other estimates and the concentration data.

resentative data sets reported in the literature were used to illustrate the performance of ESTRIP. Table II gives oral tetracycline data (4), and Table III gives data collected after intramuscular haloperidol (5). The input of data during the operation of ESTRIP is illustrated in Figs. 3 and 4. The input format for the time–drug concentration values of the tetracycline data is:

9900 Data 10,0,0,1,.7,2,1.2,3,1.4,4,1.4,6,1.1,8,.8,10,.6,12,.5,16,.3

To conserve core, the figures are typed in with no spaces between data pairs and with a minimum number of individual data statements.

RESULTS

Tetracycline Data—These data were used to illustrate the operation of ESTRIP (Fig. 3) since they also were used to illustrate the operation of CSTRIP (3). The output resulting from both analyses was virtually identical. (ESTRIP analysis of the spectinomycin data used to illustrate CSTRIP performance also yielded a virtually identical output.)

Haloperidol Data—The output resulting from ESTRIP analysis of data collected after the intramuscular administration of haloperidol is given in Fig. 4. These data were described well by both the sum of four exponentials and the sum of five exponentials. Wagner (5) fitted them to the sum of four exponentials. A comparison between his estimates (graphical and with AUTOAN, a program that incorporates nonlinear least-squares analysis) and those produced by ESTRIP is given in Table IV.

The estimates given by ESTRIP for the As Data Is and the Force Thru 0,0 options were the same since only two data pairs were used in calculating A_4 and B_4, one of which was the 0,0 pair. These fits were comparable to those obtained by Wagner using a graphical method. However, the fit produced by the Best Fit option of ESTRIP included a lag time and was different from and slightly better than the AUTOAN fit of Wagner (5). An estimate of lag time was not included in the AUTOAN fit. The lag time obtained by ESTRIP was 0.145 hr (8.72 min).

ESTRIP usually gives results comparable to or better than graphical techniques and provides accurate parameter estimates. In addition, since this program is written in BASIC, it may provide a more readily available means of analysis than does CSTRIP, which is in FORTRAN IV. The primary disadvantage of ESTRIP compared to CSTRIP is the longer computing time required, because of the different computer languages being used.

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