Per Cent Absorbed Time Plots Derived from Blood Level and/or Urinary Excretion Data

Sir:

Dominguez and Pomerene (1) derived an equation, which had a form similar to Eq. 1, for calculating the rate of absorption as a function of time from blood level data

$$\frac{dA}{dt} = V\left(\frac{dC}{dt} + K.C\right) \qquad \text{(Eq. 1)}$$

Here, dA/dt is the rate of absorption or the rate of appearance of the substance in the blood, V is the apparent volume of distribution, C is the blood level in concentration units at time t, dC/dt is the slope of the blood level time curve at time t, and K is the first-order rate constant for loss of drug from the volume of distribution.

The assumptions behind Eq. 1 are: (*a*) equilibrium between drug in blood and other fluids of distribution is maintained; (*b*) V and K are constants, independent of time, over the time interval Eq. 1 is applied; and (*c*) the compound measured in the blood is the same compound as that absorbed (*i.e.*, A, in weight units, and C, in concentration units, refer to the same compound).

Nelson (2) derived Eq. 2 which may be used for calculating the rate of absorption as a function of time from urinary excretion data

$$\frac{dA}{dt} = \frac{1}{f}\left(\frac{1}{K}\cdot\frac{d^2A_e}{dt^2} + \frac{dA_e}{dt}\right) \qquad \text{(Eq. 2)}$$

Here, f is the fraction of drug reaching the circulation which is excreted unchanged in the urine, d^2A_e/dt^2 and dA_e/dt are the second and first derivatives, respectively, of a plot of cumulative amount of unchanged drug in the urine against time, and dA/dt and K have the same meaning as above. dA_e/dt is the rate of excretion at the time when the cumulative amount excreted is A_e. Theoretically, excretion rate is directly proportional to blood level (3); hence, substitution of $(1/V.K.f).(dA_e/dt)$ for C in Eq. 1 yields Eq. 2.

The assumptions behind Eq. 2 are: (*a*) equilibrium between drug in blood and other fluids of distribution is maintained; (*b*) f, K, and the renal clearance ($f.K.V_d$) are constants, independent of time, over the time interval Eq. 2 is applied; (*c*) $dA_e/dt = f.dA_e'/dt$ where dA_e'/dt is the rate of elimination of the drug from the volume of distribution by all processes; and (*d*) the compound measured in the urine is the same compound as that absorbed (*i.e.*, both A and A_e are weight units of the same compound).

The difficulties experienced in using Eqs. 1 and 2 are: (*a*) values of V and f are only determined, even with reasonable accuracy, by means of intravenous studies; (*b*) the second derivatives, d^2A_e/dt^2, are difficult to obtain with accuracy.

We wish to report that per cent absorbed–time plots may be derived directly from suitable blood level and/or urinary excretion data obtained following oral or parenteral administration of a drug without knowing the values of V, f, or d^2A_e/dt^2.

Integration of Eq. 1 between the limits $t = o$ and $t = T$ yields Eq. 3

$$A_T = V\left(C_T + K\int_{t=o}^{t=T} C.dt\right) \qquad \text{(Eq. 3)}$$

Here, A_T is the amount of drug absorbed from time of administration to time T, C_T is the blood level at time T, and the integral is the area under the blood level time curve between time zero and time T. Equation 3 has been previously published (4).

Integration of Eq. 2 between the limits $t = o$ and $t = T$ yields Eq. 4

$$A_T = \frac{1}{f}\left(\frac{1}{K}\cdot\frac{dA_e}{dt} + A_e\right) \qquad \text{(Eq. 4)}$$

Rearrangement of Eqs. 3 and 4 yields Eqs. 5 and 6

$$\frac{A_T}{V} = C_T + K.\int_{t=o}^{t=T} C.dt \qquad \text{(Eq. 5)}$$

$$f.A_T = \frac{1}{K}\cdot\frac{dA_e}{dt} + A_e \qquad \text{(Eq. 6)}$$

Equations 5 and 6 are those suitable to prepare per cent absorbed–time plots from blood level and urinary excretion data, respectively. The method using blood level data is as follows. Successive values of the righthand side of Eq. 5 are calculated from the time of administration ($t = o$) to some time after the peak in the blood level time plot (the areas may be estimated with the trapezoidal rule). The values progressively increase, then reach a maximum or asymptotic value. When the individual values are expressed as percentages of the maximum or asymptotic value, the results are per cent absorbed values to various times T. The method using a cumulative amount excreted–time curve is as follows. For the initial part of the plot, values of $\Delta A_e/\Delta t$ and the amount excreted at the midpoint of the interval, A_e, are calculated. The operations dictated by Eq. 6 are then performed to yield values of $f.A_T$. The values pro-

gressively increase, then reach a maximum or asymptotic value. When the individual values are expressed as percentages of the maximum or asymptotic value, the results are per cent absorbed values to various times. Theoretically, the maximum or asymptotic value of the right-hand side of Eq. 5 is $K.\int_{t=o}^{t=\infty} C.dt$ and of Eq. 6 is $(A_e)_\infty$, where $\int_{t=o}^{t=\infty} C.dt$ is the area under the blood level time plot from $t = o$ to $t = \infty$, and $(A_e)_\infty$ is the amount of unchanged drug excreted in the urine in infinite time. The methods are independent of the values of V and f since these values cancel out when the percentages are calculated. The per cent absorbed value so calculated is the cumulative amount absorbed to time T expressed as a percentage of the total amount of drug which is absorbed (not as a percentage of the dose).

When the cumulative percentages absorbed are plotted against time, the resulting plots may contain linear segments; the slope of such a linear segment is the absorption rate in per cent/hour. If the plot is curved, or contains curved and linear segments, it may often be resolved to yield the components of the rate $d\%A_T/dt$. In this way the model which applies to a particular set of blood level or urinary excretion data can be determined accurately. The method may also be applied to problems in chemical kinetics involving consecutive and/or simultaneous first-order and zero-order reactions.

The process of obtaining the per cent absorbed–time plots from blood level data has been automated in two ways. In the first method, the blood level data are plotted on suitable graph paper and the points joined with a smooth line using a special conducting ink. Using a curve-follower, an analog computer was programmed to perform the operations dictated by Eq. 5 and to plot the result on another piece of graph paper. The asymptotic value is estimated from the plot, the values of A_T/V are obtained from the plot, and then expressed as a percentage of the asymptotic value. In the second method, the blood level–time values are fed to a suitably programmed digital computer. The computer calculates the cumulative areas, using the trapezoidal rule, then performs the necessary operations shown in Eq. 5. The print-out contains the values T, C_T, $\int_{t=o}^{t=T} C.dt$, and $\left[C_T + K.\int_{t=o}^{t=T} C.dt\right]$. The latter are then expressed as percentages of the asymptotic or maximum value of the same function to yield the cumulative per cent absorbed values.

Per cent absorbed–time plots derived from *in vivo* data are the optimum data to correlate with per cent released time plots derived from *in vitro* testing.

Future publications will illustrate applications of these methods in detail.

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(3) *Ibid.*, **50**, 181(1961).
(4) Wagner, J. G., Carpenter, O. S., and Collins, E. J., *J. Pharm. Exptl. Therap.*, **129**, 101(1960).

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Book Notices

Recent Advances In Pharmacology. 3rd ed. By J. M. ROBSON and R. S. STACEY. Little Brown and Co., 34 Beacon St., Boston 6, Mass., 1962. x + 406 pp. 15 × 23.5 cm.

The reader of this book will find several areas of recent progress in pharmacology discussed in some detail through the efforts of the authors and nine contributors. The chapter on pharmacologically active substances in the central nervous system requires 38 pages. One-third of the chapter is devoted to catechol amines and 5-hydroxytryptamine; 5-hydroxytryptamine is later treated in a separate chapter of 30 pages and the catechol amines in another of 25 pages. Other chapters deal with pyschotropic drugs, pharmacologically active polypeptides, hypoglycaemic agents and diabetes mellitus, diuretics and electrolyte balance, newer steroids, cholesterol, hypotensive drugs, bacterial chemotherapy, new drugs in the treatment of tropical diseases, and hypnotics, anticonvulsants, analgesics, and antitussives. References to pertinent literature follow each chapter.