protio- or deuterio-succinic acid and vitamins in media above 98% D_2O, growth was obtained at all succinic acid concentrations, but growth is much better at lower concentrations of succinic acid (Table III). Withdrawal of the vitamin mixture leads to reduced growth and a reduction in the size and abundance of floating mycelia. The effect of changes in phosphate concentration, vitamin withdrawal, and various additives on the production of deuteriated alkaloids is under investigation.

SUMMARY

C. purpurea, strain 47A, does not require a carbohydrate carbon source in order to metabolize and produce alkaloids in ordinary water or 50% D_2O in the presence of succinic acid. The total amount of alkaloid produced increases with increasing succinic acid concentration. Above 75% D_2O, a carbohydrate carbon source becomes indispensable, and fully deuteriated *Claviceps* can be successfully cultured.

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Release of a Drug from a Dosage Form

By H. STELMACH, J. R. ROBINSON, and S. P. ERIKSEN

The complete interpretation and use of absorption, distribution, and excretion data depend upon an understanding of the mechanism of release of the drug from the dosage form and then on the ability to utilize this information to predict its effect *in vivo*. An analog computer program suitable for using blood *versus* time data as an input and producing the *in vivo* dosage form availability *versus* time pattern as its output has been developed, tested on synthetic problems, and used to analyze published blood data for a sustained-release form and a multiple-dosage regimen of sulfaethylthiadiazole (SETD) and solution, capsule, and tablet forms of acetylsalicylic acid. Similar programming ideas have produced a program able to predict, for known systems, the effect of changes in the *in vivo* release patterns on the absorption, distribution, and excretion picture.

SINCE the advent of sustained-action, sustained-release, and delayed-availability dosage forms, considerable effort has gone into the collection and correlation of absorption, distribution, and excretion data for many drug substances (1). Proper correlation and use of these data have depended mainly upon the use of exponential (first-order) approximations for the obviously very complex natural processes that occur within the body. A tacit but simplifying assumption in most of these approximations is that the drug is either all available immediately (administration of solution to the gut or by injection), or that it becomes available in a manner described by some ordinary linear differential equation (2). In the case of I.V. solutions, while the slug of drug injected is not *truly* a well-defined concentration, uniform at time 0, as is usually assumed, the other rates (absorption and excretion) involving the drug are so much slower than the rate of injection and mixing that the error in this assumption may be safely neglected. A solution in the gut, however, and even more so for other less rapidly available dosage forms as well as for more exotic administration sites, is not and does not become a uniform concentration; nor is it reasonable to assume that the availability of a drug from it follows any linear ordinary differential equation (save perhaps a series approximation)—at least not one that can be theoretically formulated without some actual release or availability data being obtained directly in the GI tract. The approximations currently in use for calculating

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sustained-release requirements seem the more remarkable then in that although the rotating bottle (or other *in vitro* testing system) (3) was designed only as a control device, not as a gut simulator, it either *does* simulate the gut fairly well or the requirements for sustained release are such that any solution-controlled test would give suitable relative results. The desired blood picture *is* obtained from dosages tested in this manner.

It has become increasingly apparent as more careful studies are done on the effect of solution rates that the simplifying assumptions used in the classical solution-diffusion studies do not hold well for all cases, and other parameters often become quite important (*i.e.*, stirring rate; see for instance *Reference 4*). Thus, it would appear that if one considered only one aspect, a constant shear or totally diffusion-controlled system, while perhaps suitable for a first approximation, is not necessarily the best *in vitro* test.

In all these studies, researchers have been hampered by incomplete knowledge concerning the true release pattern of a drug-containing dosage form *in the gut* and/or some suitable method to utilize *in vitro* solution or availability data to predict its effect on the *in vivo* system in any exact way.

This report describes investigations made into the use of analog computation as a means of solving both these problems, *i.e.*, determining the apparent dosage form–gut release pattern from *in vivo* data, and conversely, predicting the effect of various gut release patterns on the *in vivo* absorption, distribution, and excretion (ADE) kinetics.

EQUIPMENT

The work described was performed on a 24-amplifier (8-integrator) 100-v. patchboard computer made by the Applied Dynamics Corp., Ann Arbor, Mich. Two *X-Y* recorders were used in the study, an Electro Instruments potentiometric recorder (model 101-1518) and a Moseley potentiometric recorder (model 2D-2AM) fitted with a type F-1 photoelectric line follower and a retransmitting slide-wire.

BACK CALCULATION OF DOSE AVAILABILITY PATTERNS

The most common, and for our purposes, the most useful mathematical model for ADE kinetics is

$$G \xrightarrow{k_a} B \xrightarrow{k_e} E \qquad \text{(Eq. 1)}$$

where G, B, and E represent concentration (or perhaps activities?) of the drug in the gut, blood, and excreta, respectively.[1] (A more complete model will be discussed in the *Appendix*.) The differential equations for this model are

$$dG/dt = -k_aG \qquad \text{(Eq. 2}a\text{)}$$

$$dB/dt = k_aG - k_eB \qquad \text{(Eq. 2}b\text{)}$$

$$dE/dt = k_eB \qquad \text{(Eq. 2}c\text{)}$$

and from these a general, unscaled, computer diagram may be drawn. It is in the implied assumption that the total dose becomes available at $t = 0$ (*i.e.*, $G = G_0$) that the simulation breaks down, however. There is at least one other step that must be considered for most drugs administered in a dosage form (D), *i.e.*,

$$D \overset{k_r}{\rightsquigarrow} G \xrightarrow{k_a} B \xrightarrow{k_e} E \qquad \text{(Eq. 3)}$$

although the mathematical form of the release from $D \rightarrow G$ is unknown, and thus the complete computer program cannot be written. The first step of the operation described by Eq. 1 is not operating simply from some initially uniform gut pool at concentration G_0 as is usually assumed for calculation purposes, but is instead operating from a varying pool whose total available drug is increasing slowly with time. If this pool's available drug–time relationship can be defined, the precise form of the $D \rightarrow G$ reaction should be determinable.

It is possible to rewrite Eqs. 1 and 2 so that G is included in terms of the quantity of drug absorbed into the blood (x) [rather than the quantity of drug present in the gut pool at any time (G)], and instantaneous quantity of drug added from the dosage form [some unknown function, $f(k_r,D)$], as a function of time

$$dx/dt = k_a\left[\int_0^t f(k_rD)dt - x\right] \qquad \text{(Eq. 4)}$$

This relationship is essentially that used for the solution of kinetic situations where x is, in those cases, the product of the reaction, and the function $\int_0^t f(k_rD)dt$, the initial concentration of the reactant, a constant. In our case the function $\int_0^t f(k_rD)dt$ is not necessarily a constant. Most likely it varies in some unknown way with time. Equation 4 implies then that the rate of loss from the gut is equal to the k for absorption times the total quantity of drug provided by the dosage form $\left[\int_0^t f(k_rD)dt\right]$ minus the amount already absorbed (x).

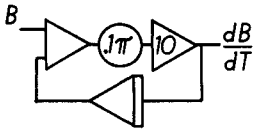

Fig. 1.—The computer program for the differentiator used in this study.

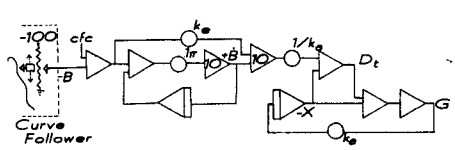

Fig. 2.—The computer program used to solve Eq. 6. (See text.)

[1] For our purposes, one need not be concerned with compartment volumes or with more complex models at this point. It is sufficient to note that enough systems and drugs *are* satisfactorily approximated by the model given that for our purposes Eq. 1 will be used as is.

It is feasible that with a function generator of some type to simulate the availability function, Eq. 4 could be programmed, and once that was done, the remaining program (of the usual form) would then be able to simulate the effects of any change in $f(k_rD)$ on the drug contained in any compartment. Conversely, it should be possible to plot $f(k_rD)$ as a computer output if other pieces of biologic data are available. We shall consider two types of biologic data as representative examples, blood level and cumulative urine data.

Blood Level Data.—If blood level–time data are used, rewriting Eq. 2*b* in terms of Eq. 4 and defining

$$D_t = \int_0^t f(k_rD)dt \qquad \text{(Eq. 5)}$$

one obtains

$$D_t = \frac{\dot{B} + k_eB}{k_a} + x \qquad \text{(Eq. 6)}$$

as an equation for the integral we seek, all parameters of which can be electronically simulated from or with the *B versus* time data available.

Differentiation is not an operation an analog computer does easily, but several circuits *are* available that approximate it. The one shown in Fig. 1 is the one we have found suitable for the slow differentiation we require (5). The transfer function for this circuit is $s/[1 + (s/\pi)]$,[2] where π is a damping factor in the differentiator circuit. By adjusting π to a value of about 7.5, a sufficiently noise-free yet accurate differentiation could be obtained for our data. This differentiator solves the function

$$dB/d\tau = \left(\frac{1}{\pi}\right) dz/d\tau + z \qquad \text{(Eq. 7)}$$

in the time, τ, domain and thus as the value of $\pi \to \infty$, the output of the differentiator (z) approaches the desired derivative, $dB/d\tau$.

Equation 6 can be solved by a combination of indirect solution and simulation to produce the desired integral, D_t, as a function of time; the unscaled computer program is shown in Fig. 2. The input data for B are supplied from the curve follower which produces a voltage proportional to B, normalized to the computer reference 100 v.

A demonstration of the performance of the program in Fig. 2 is shown in Fig. 3 (*a*, *b*) and Fig. 4 where a standard program simulating the model of Eq. 1 has been used to generate G, B, and E, although E is not shown here. The differentiator circuit may be used either by direct connection of the B output from the generator circuit at point ⟨X⟩ or by using the curve follower input at ⟨X⟩. This latter method, a fair approximation of the use of blood data, is accomplished by recording *B versus t* with one recorder, while the curve follower is used as the input of D_t, in the case of the step function, input form (*b*) (see under *Cumulative Urine Data*), or by manually impressing +, 0, or −100 v. on the D_t input to obtain a square wave [input form (*a*)]. The recorded curve of *B versus* time is then used as the B input by tracing it with the curve follower (after disconnecting the

[2] The transfer function is given in the customary Laplace transform notation. For a discussion of transfer functions and the Laplace notation, see *Reference 6*. Other differentiators may be found in *Reference 6*, p. 145 ff.

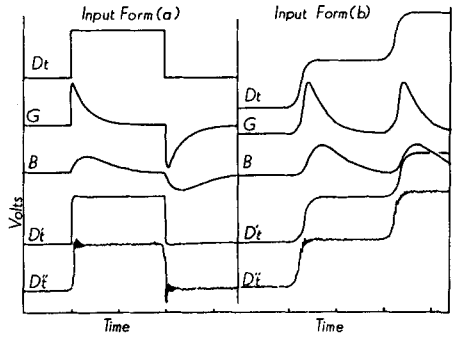

Fig. 3.—Demonstration of the performance of the computer program shown in Fig. 4. Input form (*a*), the step function; input form (*b*), the smoothed step function. Curve D_t, the actual input shape, G, the gut concentration, B, the blood concentration, D_t', the availability calculated with direct connection, D_t'', the availability calculated with use of the curve follower.

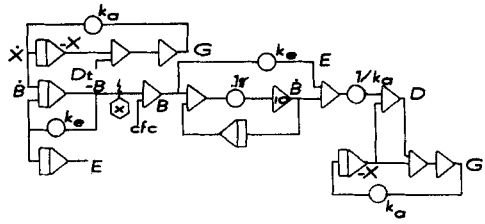

Fig. 4.—Circuit designed to test the effects of various dose input forms.

generating source at ⟨X⟩). The reconstituted values of D_t *versus* time are shown in the figure (direct connection, D_t'; curve follower, D_t'').

The input to the generating circuit is accomplished in such a way that any function D_t *versus* time may be inserted, using a predrawn D_t *versus* time curve and the curve follower. This portion of the circuit of Fig. 4 will be discussed under *Use of Nonlinear Inputs.*[3]

Two forms of D_t input were tested and are shown in Fig. 3, the square wave [form (*a*)] and the smoothed step function [form (*b*)]. The direct connection of the B output produces an accurate reconstitution of D_t (labeled D_t') for both types of input. Using the curve follower, the reconstituted D_t from input form (*a*) is noisy but accurate (labeled D_t''), but is both accurate and undistorted for input form (*b*). The sharpness of the corners and the steepness of the lines in input (*a*) makes the curve follower an inaccurate tool for this type of input, but for continuous smooth curves as in (*b*) (more like those we expect for ADE data), it follows all but the steepest slopes.

As examples of the use and utility of the curve follower and the program shown in Fig. 2, blood level–time data from three types of dosages were analyzed: sustained action, initial plus repeated maintainance doses (both of SETD), and single

[3] Because of mechanical limitations, a curve follower correction (CFC) must be used *whenever* the curve follower is used in order to make the curve tracing zero correspond to zero output from the curve follower.

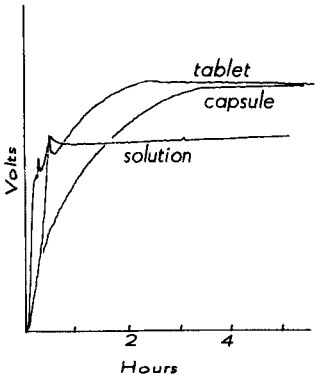

Fig. 5.—*In vivo* availability curves for three forms of aspirin: solution, tablet, and capsule.

doses of acetylsalicylic acid in solution, tablet, and capsule form.

The *in vivo* availability curves for aspirin are shown in Fig. 5. The solution data (7) were used to estimate the k_a, and the average k_e estimated using capsule (8) and tablet (9) data as well. The mean values used were k_a = 8.34 hr.$^{-1}$ and k_e = 0.0837 hr.$^{-1}$. Because the shape of the blood–time curves over the first 0.5 hr. could only be estimated for the tablet and capsule cases, the reliability of the availability curves in this region is questionable. The general shapes of the availability curves follow one's expectations, however. The more rapid availability of the tableted drug is probably due to not having to be washed out of the remaining capsule half in order to become available.

With the sequential step dosing such as these data describe, the blood picture *should* show a series of peaks and valleys. [See Fig. 3 (*b*) and *Reference 14*.] The interpretation of an average availability curve obtained from a time-averaged blood curve must be viewed as only a rough approximation. For a *complete* availability curve to be drawn, the complete blood picture must be used.

In Figs. 6 and 7 are shown the results of availability analysis of two forms of SETD. One single dose of 2 Gm. followed by 0.22 Gm. every hour for 8 hr. produced blood levels consistent with the availability curve shown in Fig. 6 (10). Because it is poorly soluble in water, estimates of k_a by available means (including electronic curve fitting) produce only very rough approximations. In addition, k_e appeared to be different for some dosage forms than for others (11).[4]

The effect of the extremes of k_a and k_e was tested on the reported blood levels with the results shown. Again data at time periods less than 1 hr. are in some doubt, but even though the precise shape of the peak at 45–60 min. depends somewhat on where one draws the blood level curve, the bump seems significant and expected. The dependence of the initial region on the k_a and the later region on the k_e is marked. The fact that some 44% of the total dose was given at intervals after 1 hr. suggests that even a larger k_a than 4.0 hr.$^{-1}$ (and/or a larger k_e than 0.062 hr.$^{-1}$) would probably be more correct. One suspects that the latter is the more correct as the availability curve

[4] The data for subjects in Table I (10) were averaged before use.

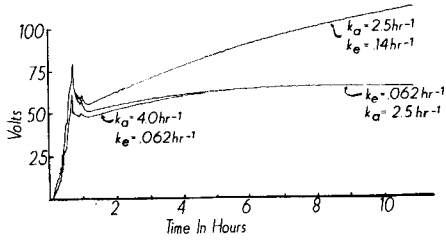

Fig. 6.—*In vivo* availability curves for repeated doses of SETD. Two grams initially followed by 0.22 Gm. hourly for 8 hr. The rate constants used are for the model shown in Eq. 1 and represent the extremes of those found to describe the data.

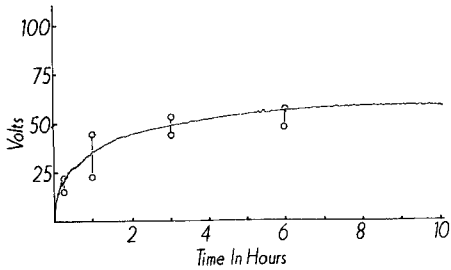

Fig. 7.—*In vivo* availability curves for sustained-action forms of SETD. The superimposed points are the *in vitro* release rates for the product tested as measured by the rotating bottle method. (The high and low limits are shown.)

should become horizontal at something over 8 hr. (rather than 7 hr. as here).

Availability analysis of a sustained-action form (using the best k_a and k_e data) produced the curve shown in Fig. 7 (12). Superimposed on this graph are the limits of the rotating bottle release rates reported for this material by Swintosky. The comparison of the *in vitro* control method and the *in vivo* availability curve is remarkable but not unexpected, as the sustained-action form seems to produce the blood levels for which it was designed and with a release rate that the rotating bottle seems to verify.

The requirements for the use of this program might be summarized here, although it should be obvious from the program. It is only required that whatever model is used adequately describe the blood picture, *i.e.*, the fact that there are many other things contributing to the absorption and excretion of the drug does not invalidate the procedure. The fact that these experimental studies are adequately described by only two constants (although each is made up of several k terms) in this case is sufficient. All the constants required to describe the model over the time range used must be known, however, in order to obtain a true picture of the desired function $\int_0^t f(k_r D)dt$.

Cumulative Urine Data.—If cumulative urine data are available, more information is required to solve the problem completely, although it is still solvable. There are at least two approaches here, using E *versus* t data and the same simplified model shown in Eq. 1. Rewriting Eq. 2 in the manner discussed above,

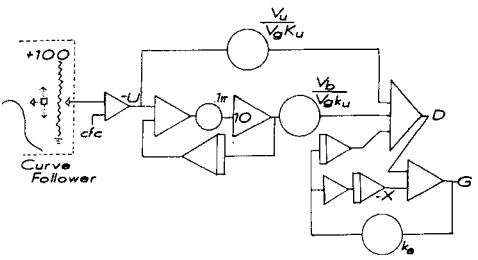

Fig. 8.—The computer program for the solution of Eq. 12 using cumulative urine data.

$$D_t = \frac{1}{k_a k_e}(\ddot{E}) + \frac{1}{k_a}(\dot{E}) + x \quad \text{(Eq. 8)}$$

This equation requires two differentiations, an undesirable series of operations for an analog computer. If one instead used a mass balance form and considered a further complication where other pathways also were taken into account,[5] *i.e.*,

$$G \xrightarrow{k_a} B \xrightarrow{k_e} E \qquad \text{(Eq. 9)}$$
$$\xrightarrow{k_u} U$$

one can make use of the mass balance relationship

$$V_g D_t = V_g G + V_b B + V_e E + V_u U \quad \text{(Eq. 10)}$$

where $V_{g,b,e,u}$ are the associated volumes of the gut, blood, excreta, and urine. The relationships of the excreta and urine can be simplified by determining the fraction of the total drug excreted by way of the urine, K_u, where

$$K_u = \frac{V_u U}{V_u U + V_e E} \quad \text{(Eq. 11)}$$

when one recalls that

$$G = -\int_0^t k_a(Dt - x)dt$$

and that

$$\dot{U} = k_u B$$

substitution of these definitions and Eq. 11 into Eq. 10 produces

$$Dt = -k_a \int_0^t (Dt - x)dt + \frac{V_b}{V_g k_u}\dot{U} + \frac{V_u}{V_g k_u} U \quad \text{(Eq. 12)}$$

and the desired function D_t as a function of time should be obtainable from the program shown in Fig. 8.

The need for volume terms in this equation requires considerably more interpretation, and the urine data procedure will be discussed elsewhere (13).

The availability curves produced by this analog program are based upon identical concentration units as those of the blood data inserted as B (1 v. = 1 mg./100 ml. in the case of SETD data and the aspirin data). In terms of the *actual quantities* of drug, proper interpretation of some "volume" terms is required. For the purposes for which the data are used here, no discussion of apparent distribution or gut or other volumes are required; thus, the ordinates on Figs. 5–7 have been left as volts.

[5] The blood time program does not need correction for other pathways of loss as these are lumped into the found value of k_e. Using the model of Eq. 9, Eq. 6 becomes

$$D_t = [\dot{B} + (k_e + k_u)B]/k_a + x$$

and the previous k_e term has become $(k_e + k_u)$.

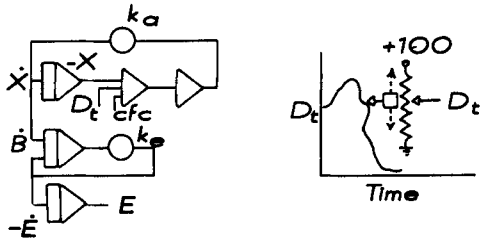

Fig. 9.—The computer program for the use of availability data (nonlinear) in testing its effect on the ADE performance of a known drug.

USE OF NONLINEAR INPUTS TO STUDY THE EFFECTS OF A DOSAGE AVAILABILITY PATTERN ON AN *IN VIVO* SYSTEM

While the determination of the apparent *in vivo* drug availability pattern is our main concern, the same general method can be used to study the effect of a particular availability pattern on the ADE performance of a drug whose absorption and excretion constants are known. As already mentioned in the discussion of Fig. 3 (*a*, *b*) and Fig. 4, rewriting Eq. 4 permits the gut dose input to be varied in any theoretical or experimentally determined way. The analog program as shown in Fig. 9 can be used to simulate Eq. 4 as it is applied to the simple model of Eq. 1. The performance of this input method was shown and discussed in Fig. 3 (*a*, *b*) and Fig. 4 and under *Back Calculation of Dose Availability Patterns*. The reproduction of the blood levels from sequential step inputs (*i.e.*, repeated doses), as shown in that figure, fit the expected shape and the published data (14).

In summary, several instrumental and programming innovations have made it possible to use *in vivo* blood level data for analog computation to estimate the apparent *in vivo* release or availability pattern for a drug in a dosage form (and have suggested similar use of urine data). Information of this kind should permit careful and searching investigations into the mechanism of release from dosage forms as well as the functioning and control of *in vitro* test and gut simulation methods and equipment. Similar innovations and techniques will permit estimates to be made of the absorption, distribution, and excretion effects of various dose availability patterns, this both for the purposes of control and improvement of delayed availability dosage forms.

APPENDIX

As there are several manners of considering analog computation and it is felt that the advantages of one of them are not sufficiently apparent to all, simulation programming as opposed to direct or indirect calculations (or approximation) with the analog (and for that matter digital) computer deserve some discussion. Direct calculation programming does

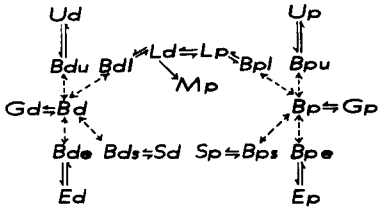

Fig. 10.—The descriptive model upon which the simulated human absorber, distributer, and excreter program (Fig. 11) has been built.

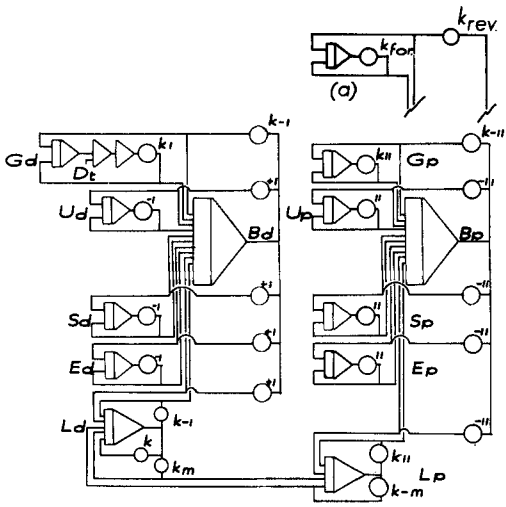

Fig. 11.—The analog computer program for a simulated human absorber, excreter, and distributer. Part (*a*) represents the building block needed for adding another compartment to the scheme.

not take advantage of the main advantage of analog computation: that of enabling one to study the relative importance of each of the various independent but interrelated parts of the system. This advantage permits the analog computer equipped experimenter to determine easily and quickly those parts of the model that may safely be lumped, those parts that may be neglected, and those parts that may be incorrect and should be changed. The first two operations may be done on the digital computer also (although the changes and their effects are much easier to see and make on the analog), but the latter is only possible with any facility using analog computation. (It is often a difficult problem with direct mathematical solution also.) One should not confuse statistical correlations, which are measures of fit, with implications of how the models should be changed. These are not the same thing.

Simulation in its best aspects provides another advantage, that of using building blocks as a simplified approach to programming, *i.e.*, having only to attach or turn on another block when another pathway is observed or suspected. For ADE kinetics, the fact that all systems noted to date can be suitably approximated by simple exponential (linear or first-order) terms—in many cases only complicated by reversibility or second-order terms—

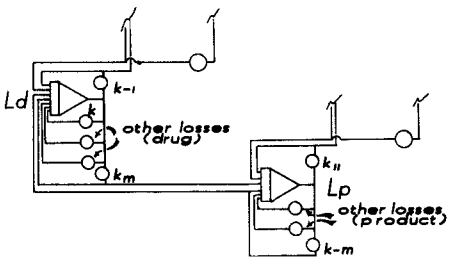

Fig. 12.—The changes in the program of Fig. 11 to enable other loss pathways in the liver to be accounted for (involving either the drug or its product).

simplifies the building blocks for each compartment to the one shown in Fig. 11 (*a*).

The use of these building blocks is shown in Figs. 10 and 11 for a complex reversible system involving a drug (*d*) and its unique product (*p*), both of which are stored (*S*), excreted by two paths (*E* and *U*), and absorbed as such from the gut (*G*). This program was drawn for a drug such as acetone (product isopropanol) that enters the general metabolism through the liver (*L*) ($\xrightarrow{k}$ metabolic product, *MP*). The blood distribution times from the site of absorption to the site of action are noted by dashed lines but are assumed small with respect to the other reaction times.[6] The analog program for this is shown in Fig. 11 and includes three basic building blocks: that for the liver (or metabolizer), the blood, and the compartments [as shown in Fig. 11 (*a*)]. The function of the blood portion is apparent from the figure; the compartment blocks may be added or deleted as required; and other loss routes in the liver, either of the drug or the product, are added as shown in Fig. 12.

In this manner, a simulated human absorber, distributer, and excreter may be assembled to any degree of complexity, limited only by the demand of the problem, the knowledge of the experimenter, and the resources of the institution.

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[6] Circuits for the approximations of delay times are available but needlessly complicate our picture. (See for instance *Reference 6*, p. 45.)