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SOME MATHEMATICAL ASPECTS OF CHEMOTHERAPY: I. ONE-ORGAN MODELS

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A model of the processes occuring in the exchange of a drug between capillary plasma, extracellular space and intracellular space is developed. This leads to an interesting set of differential difference equations, one of which is an integrodifferential equation, another a partial differential equation. Under certain conditions, these may be simplified to a set of ordinary differential equations. The application of Laplace transform techniques to the solution of these equations is discussed.

1. *Introduction.* Mathematics plays a fundamental role in the physical sciences because it furnishes the possibility of setting up realistic models of physical phenomena which can then be treated by uniform techniques.

This has not generally been true of the fields of biology and medicine. Often the realistic models have defied the state of the art of mathematics, or the oversimplified models that have been treated have furnished little insight into actual biological phenomena.

The present paper is the first of a series of papers in which we wish to study qualitative and quantitative aspects of chemotherapy. Specifically, what we wish to study is the distribution of a compound in the organs of the body after its injection into the blood stream.

These problems are similar in many respects to a class of problems arising in mathematical economics in connection with multistage production processes and generally in the domain of "input-output" analysis. The biological problems are, however, in many ways more complex.

It turns out that the study of either dynamic or static (steady state) behavior of the organs of the body, arranged in series-parallel networks, bears a certain resemblance to the operation of complexes of interdependent industries, and also to the cascade processes encountered in isotope separation or in the operation of oil refineries. These matters will be discussed subsequently. Here, in this initial paper, we shall study a relatively simple system consisting of the heart and one organ.

At the moment, we are concerned with the purely descriptive phase of the study of these life processes. As we shall see, one of the advantages derived from the formulation of mathematical models on even this moderate plateau of realism is the light it throws on the need for further experimental work which will yield the data required for actual numerical results.

At the moment, we wish to consider only the analytic aspects. Subsequently, we wish to formulate multi-organ models and apply analogue and digital computing techniques to the solution of various linear and nonlinear sets of equations which arise from them.

Following this phase of our program, we wish to turn to our primary objective, the study of control aspects of these processes. Our ultimate aim is to determine chemical injections with optimal specific properties.

From the mathematical point of view, the study of these problems is quite interesting due to the presence of novel features not usually found in the study of mathematical physics or mathematical economics. To begin with, there are a number of difficulties present at the very outset when we attempt to set up a mathematical model. Next, we find that the built-in periodicity and time lag furnished by the circulation of the blood leads to differential difference equations involving partial derivatives. Furthermore, the time lag appears in the boundary conditions! Although these can be treated by Laplace transform techniques under certain simplifying assumptions which yield linear equations, more detailed models yield nonlinear equations. The numerical solution of large-scale systems of differential difference equations is not a trivial matter. In particular, the computer memory requirements may become excessive. The equations resulting from the Laplace transformation are also of interesting type. They are integrodifferential equations with boundary conditions of two-point type.

The question of determining what type of steady state results hinges upon the investigation of the characteristic roots of quite complicated transcendental functions. Although the method of L. Pontrjagin (1955) can be used in some cases, in others, the matter is still unresolved. As we shall see, physical reasoning can sometimes be employed.

The reader versed in biological and physical matters will see that we have omitted a number of effects in our treatment. Our excuse is a simple one—the problem is a complicated one even at this level.

In Section 2 some physiological considerations are provided by way of background. This leads to a model of a one-organ being in which we seek to determine the concentration of a drug as a function of time and position, where the concentration satisfies a certain partial differential equation along with appropriate initial and boundary conditions. The role of the Laplace transform in effecting a solution is indicated. It is then shown in Sections 9 to 11 how many essential features of this original model can be preserved, though the problem is much simplified, through the introduction of a still further simplified model. Finally in Section 12, we show how to formulate equations for the situation in which a drug is injected into the blood stream, enters the extracellular space, and finally enters the intracellular space where it takes part in a reversible chemical reaction.

2. *Physiological considerations.* Except for two special cases, we may consider the various organs of the body as being in contact with the closed-circuit circulation as in Figure 1, with the various organs or regions of the body in parallel.

As an introduction to the quantitative study of this system, we consider the drastically simplified case of a single region with a closed-circuit blood supply. We defer consideration of mixing in the circulation until we take up the many-organ model (Jacquez, Bellman, and Kalaba, 1959). We feel that this case will illustrate the essential assumptions required to construct the model.

The region involved consists of many simply connected spaces, living cells, of various roughly similar shapes and sizes; each is separated by its boundary, the cell membrane, from a watery fluid, *the extracellular fluid*, which fills the space outside the cells. The blood supply to this region enters via a number of tubes, arteries,

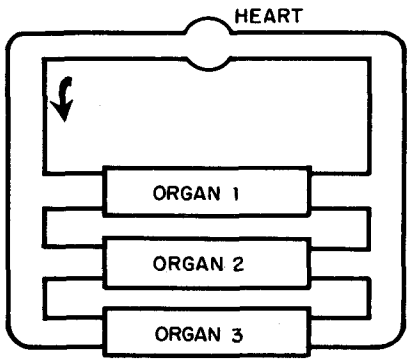

FIGURE 1. Diagram of parallel arrangement of body organs in relation to blood supply.

which branch into the small arterioles. Each of the many arterioles gives rise to many, small, thin-walled tubules, the capillaries, which pass in many directions through the extracellular space and finally join into venules which combine to form the veins which carry the blood from the region. Exchanges between the blood and and the cells of the region occur by diffusion between the blood and extracellular space and between extracellular space and *intracellular space*.

Although capillaries vary somewhat in dimensions, we may take the average capillary to be .0004 cm in radius and .04 cm long. All the capillaries to a region are not always open with the number through which blood is flowing at any one time depending on the state of the tissue. Thus, for a resting muscle only 5 capillaries per sq. mm may be open, while for stimulated muscle as many as 190 capillaries per sq. mm may be functioning. We consider only situations in which the number of capillaries open is roughly constant. The blood flowing through the capillaries consists of a suspension of cells in fluid, the plasma. The exchanges we will be concerned with will be between the plasma and extracellular space, so we will speak in terms of the plasma flow to a region.

We may now construct our model. The fully rigorous approach would be to write the differential equations of material balance taking into account the flood flow rate for each capillary, filtration and diffusion across capillary walls and diffusion in the extracellular space, and introducing the geometrical relations between all capillaries in the region and the distribution of extracellular space

in relation to cells and capillaries. The explicit statement of such a program is sufficient to indicate its sterility. A macroscopic viewpoint may be more useful. If one takes a cross section of a region, the capillaries in the cross section will be roughly uniformly distributed with their flows in various directions. From a macroscopic viewpoint, such a distribution tends to smooth out any diffusion gradients. The normal rotation of functions among various capillaries so that capillaries without any flow open up while others shut down can only add to this leveling process. Filtration across capillary walls may be neglected since it is a minor process compared to diffusion, for molecules smaller in size than inulin (Chinard, Vosburgh, and Enns, 1955; Pappenheimer, Renkin, and Borrero, 1951). The flow rates for various capillaries are not necessarily the same. We do not introduce this in the present treatment but assume one average flow rate. These considerations suggest the most important assumption of the model, that is, at any time the concentration of a material exchanging between the plasma and the region is uniform in the extracellular space. The approximate validity of this assumption is implied by the experimental evidence that the tissue-blood exchange rates for inert gases (Jones, 1950) and small ions (Conn and Robertson, 1955; Dobson and Warner, 1957; Freis, Higgins, and Morowitz, 1953) are limited by blood flow to a region and not by molecular diffusion. Thus we may conceptually lump all of the capillaries into one the length of which is l, the average length of a capillary. As with the flow rates, we disregard the effect of any possible distribution in the lengths of capillaries. The effect of this will be considered in a future paper. As shown in Figure 2, this capillary contains a volume R_p of plasma, has a surface area A_e of contact with the well-stirred extracellular

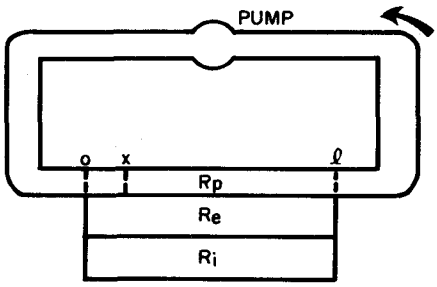

FIGURE 2. Model of a closed circulation with a single organ.

space of volume R_e, and has a volume flow rate of c. The extracellular space is in contact with the intracellular space of volume R_i and surface area A_i.

G. W. Schmidt (1952, 1953) has considered a model similar in some respects to ours for the exchange of a substance between blood and extracellular space, but has not explicitly introduced the problem of recirculation or of the possible reaction of the substance with a component of the intracellular space. R. E. Smith and M. F. Morales (1944) and Morales and Smith (1948) have treated the problem of the exchange of an inert gas between capillaries and tissues. W. C. Sangren and C. W. Sheppard (1953) have presented calculations on a model which assumed rapid mixing in the direction perpendicular to the axis of the capillary but no mixing longitudinally. Considering the anatomical distribution of capillaries and extracellular space this does not seem to be a physically reasonable assumption.

We consider first the simplest case, that of diffusion of a compound into the extracellular space. The compound is assumed not to enter the intracellular space. We shall subsequently consider both diffusion processes, as well as an active transport process.

3. *Notation.* To reduce some of the foregoing ideas to mathematical form, let us introduce the following definitions:

$u(x, t)$—concentration of drug in mass per unit volume at x in the capillary at the time t

$v(t)$—spatially uniform concentration of drug at time t in the extracellular space

c—volume rate of plasma flow in the capillary bed

k—permeability constant for capillary walls in units of lt^{-1}

l—length of capillary

R_p—plasma volume in capillary

R_e—volume of extracellular space

A_e—total surface area for diffusion between plasma and extracellular fluid

τ—the time for a particle to travel around the circulation from l to 0. If R is the plasma volume other than that in the capillary, $c\tau = R$. We neglect mixing in the heart and large vessels. This will be considered in a subsequent paper.

4. *Derivation of basic equations.* Let us now derive equations connecting $u(x, t)$ and $v(t)$. From conservation principles, we obtain the relation

$$\frac{R_p}{l} u(x, t + h)\, dx = \frac{R_p}{l} u(x, t)\, dx + (u(x, t) - u(x + dx, t))\, hc + \frac{A_e k}{l} (v(t) - u(x, t))\, h dx. \tag{1}$$

The second term on the right-hand side arises through the motion of the blood in the circulation and the last through diffusion into the extracellular space. Letting h and dx tend to zero, we obtain the equation

$$\frac{R_p}{l} u_t = -cu_x + \frac{kA_e}{l} (v - u). \tag{2}$$

where u_t and u_x denote partial derivatives with respect to t and x.

Examining the rate of change of the compound in the extracellular space, we obtain the relation

$$R_e v(t + h) = R_e v(t) + \frac{kA_e h}{l} \int_0^l [u(x, t) - v(t)]\, dx. \tag{3}$$

The integral represents the net gain in the drug in the extracellular space during the time h. This leads to the equation

$$R_e \dot{v}(t) = \frac{kA_e}{l} \int_0^l u(x, t)\, dx - kA_e v(t), \tag{4}$$

valid for $t > 0$, $0 < x < l$.

To approximate an intravascular injection we assume that a rectangular concentration wave enters the capillary at $t = 0$.

Thus, we have for initial conditions,

$$u(x, 0) = v(0) = 0, \tag{5}$$

while for boundary conditions, we have

$$u(0, t) = \begin{cases} u_0, & 0 < t \leq t_1 \\ 0, & t_1 < t \leq \tau \\ u(l, t - \tau), & t > \tau, \end{cases} \tag{6}$$

where $R_p/c < t_1 < \tau$.

The restrictions on t_1 are introduced in order to approximate an injection of duration less than one circulation time. The assumptions involved in the derivation of the equation are probably less justified if we attempt to describe events of very short duration, particularly at the beginning of the process. This would be true of an injection of such short duration that the volume of plasma occupied by drug represented a small fraction of the volume of the capillary bed. For this reason the volume of plasma occupied by drug (ct_1) is made larger than the volume of the capillary bed, (R_p).

5. *Discussion.* The problem of equations (2), (4), (5), and (6) is of an interesting and rather unique type. In particular is this true of the boundary condition, involving as it does a time difference.

To resolve this system of equations, we shall proceed formally under the assumption of existence and uniqueness of solution. Our principal tool will be that general factotum of analysis, the Laplace transform.

6. *Solution by Laplace transform—I.* To simplify the notation, let

$$y = \frac{x}{l}, \tag{7}$$

$$\theta = ct. \tag{8}$$

Substituting in (2) and (4), we obtain the equations

$$R_p u_\theta = -u_y + K(v - u), \tag{9}$$

$$R_e \dot{v}(\theta) = K \int_0^1 u\,dy - Kv, \tag{10}$$

for $\theta > 0$, $0 \leq y \leq 1$. Here K is the dimensionless constant kA_e/c.

The initial conditions then become

$$\begin{aligned} u(y, 0) &= 0, \\ v(0) &= 0, \end{aligned} \tag{11}$$

while the boundary conditions become

$$u(0, \theta) = \begin{cases} u_0, & 0 < \theta \leq \theta_1, \\ 0, & \theta_1 < \theta \leq T, \ \theta_1 = ct_1, \ T = c\tau \\ u(1, \theta - T), & t > T. \end{cases} \tag{12}$$

Introducing the functions

$$L\,[u(y,\,\theta)] = \int_0^\infty u(y,\,\theta)e^{-s\theta}d\theta = U(y,\,s),$$
$$L\,[v(\theta)] = \int_0^\infty v(\theta)e^{-s\theta}d\theta = V(s), \tag{13}$$

we see that (9) and (10) yield the equations

$$R_p sU = -U_y + K(V - U), \tag{14}$$

$$R_e sV = K\int_0^1 U(y,\,s)dy - KV. \tag{15}$$

The boundary condition in (12) transforms into

$$U(0,\,s) = \frac{u_0}{s}[1 - e^{-s\theta_1}] + e^{-Ts}U(1,\,s). \tag{16}$$

7. *Solution by Laplace transform—II.* Eliminating V, we see that U, as a function of y, satisfies the integrodifferential equation

$$U_y + (sR_p + K)U - \frac{K^2}{sR_e + K}\int_0^1 U(y,\,s)dy = 0, \tag{17}$$

with the boundary condition

$$U(0,\,s) = \frac{u_0}{s}[1 - e^{-s\theta_1}] + e^{-Ts}U(1,\,s). \tag{18}$$

Let us suppress the s-dependence momentarily and consider the problem of solving a linear functional equation of the form

$$\dot{w}(y) + aw(y) = b\int_0^1 w(y)dy, \tag{19}$$

$$w(0) = c + dw(1). \tag{20}$$

A rigorous discussion would take us too far astray. Let us assume the existence of a unique solution and see how to obtain it. Set

$$\int_0^1 w(y)dy = m, \tag{21}$$

an unknown constant. Then the solution of

$$\dot{w}(y) + aw(y) = bm \tag{22}$$

is given by

$$w(y) = fe^{-ay} + \frac{bm}{a}, \tag{23}$$

where f is a constant of integration. To obtain a relation between f and m, we return to (21). The result is

$$m = f\left[\frac{1 - e^{-a}}{a}\right] + \frac{bm}{a}, \tag{24}$$

or

$$m = \frac{f(1 - e^{-a})}{(a - b)}. \tag{25}$$

To determine the remaining constant, f, we turn to the boundary condition of (20). Having obtained the value of f in this way, the function $w(y)$ is completely determined.

Upon carrying out this program we find, after considerable computation, that

$$U(y, s) = \frac{\left[\frac{u_0}{s}[1 - e^{-s\theta_1}]\right]}{\left[(1 - e^{-sT-a}) + \frac{b(1 - e^{-sT})(1 - e^{-a})}{a(a - b)}\right]} \times \left[e^{-ay} + \frac{b(1 - e^{-a})}{a(a - b)}\right], \tag{26}$$

where

$$a = sR_p + K, \quad b = \frac{K^2}{sR_e + K}, \quad (a - b) = \frac{s^2R_eR_p + Ks(R_e + R_p)}{sR_e + K}. \tag{27}$$

8. *Solution by Laplace transform—III.* The desired solution $u(y, \theta)$ is obtained by taking the inverse Laplace transform of $U(y, s)$,

$$u(y, \theta) = \frac{1}{2\pi i}\int_c U(y, s)e^{\theta s}\,ds, \tag{28}$$

where c is a contour lying to the right of all the poles of $U(y, s)$ considered as a function of s.

One pole will always be at $s = 0$, corresponding to the steady-state solution. It is easy to see on physical grounds, but difficult to establish by analytic techniques, that the other poles will have negative real parts. The inversion of equation (26) is a difficult program analytically. However, we may check the steady-state solution by evaluating the residue at the pole $s = 0$, which yields, in view of equations (26) and (27),

$$\lim_{s\to 0} sU(y, s) = u_0 \frac{ct_1}{R_e + R_p + c\tau}. \tag{29}$$

The same result can be obtained on physical grounds from a conservation condition as follows:

$$\lim_{t\to\infty} u(x, t) = u_0 \frac{ct_1}{R_e + R_p + c\tau}. \tag{30}$$

9. *A simplified model.* In an effort to relieve some of the mathematical difficulties associated with the previous model, let us handle the x-dependence in a simplified form. We note that the appearance of the integral in equation (3) implies that diffusion into the extracellular space is determined by the difference between the spatial average concentration in the capillary and the concentration in the extracellular space. We assume there is a certain concentration of the drug at the arterial end of the capillary and another at the venous end. The diffusion into the extracellular space is to depend on the difference between the average of the venous and arterial end concentrations and the concentration in the extracellular space. This again makes the diffusion dependent on a value of the plasma concentration intermediate between the concentrations at the ends of the capillary. Figure 3 illustrates this situation.

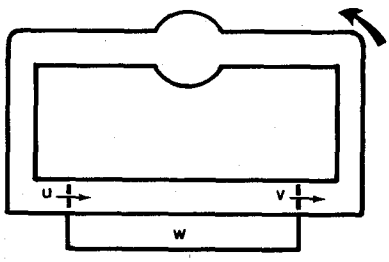

FIGURE 3. A simplified model.

$u_1(t)$—concentration of the drug at the arterial end
$u_2(t)$—concentration of the drug at the venous end
$v(t)$—concentration of the drug in the extracellular space

The equations which describe the development of the process are:

$$u_1(t) = \begin{cases} u_0, & 0 < t \leq t_1, \\ 0, & t_1 < t \leq \tau, \\ u_2(t-\tau), & t > \tau, \end{cases} \tag{31}$$

where $Rp/c < t_1 < \tau$.

$$R_e \dot{v}(t) = k_p A_e \left[\frac{u_1(t) + u_2(t)}{2} - v(t) \right], \tag{32}$$

$$R_p \left[\frac{\dot{u}_1(t) + \dot{u}_2(t)}{2} \right] = c(u_1 - u_2) - k_p A_e \left[\frac{u_1(t) + u_2(t)}{2} - v(t) \right]. \tag{33}$$

Making the substitutions $\theta = ct$ and $K = k_p A_e / c$, one obtains

$$u_1(\theta) = \begin{cases} u_0, & 0 < \theta \leq \theta_1, \\ 0, & \theta_1 < \theta \leq T, \\ u_2(\theta - T), & \theta > T, \end{cases} \tag{34}$$

where $\theta_1 = ct_1$, $T = c\tau$.

$$R_e \dot{v}(\theta) = K \left[\frac{u_1(\theta) + u_2(\theta)}{2} - v(\theta) \right], \tag{35}$$

$$R_p \left[\frac{\dot{u}_1(\theta) + \dot{u}_2(\theta)}{2} \right] = (u_1 - u_2) - K \left[\frac{u_1 + u_2}{2} - v \right] \tag{36}$$

With the initial conditions

$$u_1(0) = u_2(0) = v(0) = 0.$$

The approximation to the original set of equations is poor for processes of duration less than the capillary transit time; this is particularly true for those periods when the square wave is entering or leaving the capillary bed, for then $\frac{u_1 + u_2}{2}$ is a poor approximation to $1/l \int_0^l u(x, t)dt$. This is also a poor approximation for

K very large. For $K > 2$ this model leads to negative concentrations in the plasma leaving the capillary bed for some short period as the square wave enters the capillary bed. This may be seen from the following argument.

For $t = 0$, $u_2(0) = v(0) = 0$

Thus equation (33) reduces to

$$\frac{Rp}{2}\dot{u}_2(0) = cu_0 - \frac{k_p A_e}{2}u_0, \tag{37}$$

which rearranges to equation (38):

$$\dot{u}_2(0) = \frac{cu_0}{Rp}(2 - K). \tag{38}$$

Thus if $K > 2$, $\dot{u}_2(0) < 0$, and since $u_2(0) = 0$, this would give negative values for $u_2(t)$ for some short interval at the start of the process. In the following section we assume $K < 2$.

10. *Solution by Laplace transform.* We introduce the Laplace transforms

$$L\,[u_1(\theta)] = U_1(s), \tag{39}$$

$$L\,[u_2(\theta)] = U_2(s), \tag{40}$$

$$L\,[v(\theta)] = V(s). \tag{41}$$

In view of the equations of Section 9, these transforms satisfy the equations

$$U_1(s) = \frac{u_0}{s}[1 - e^{-s\theta_1}] + e^{-sT}U_2(s), \tag{42}$$

$$R_e s V(s) = K\left[\frac{U_1(s)}{2} + \frac{U_2(s)}{2} - V(s)\right], \tag{43}$$

$$\frac{R_p s}{2}[U_1(s) + U_2(s)] - \frac{R_p u_0}{2} = U_1(s) - U_2(s) - K\left[\frac{U_1(s)}{2} + \frac{U_2(s)}{2} - V(s)\right]. \tag{44}$$

If next we solve the system of equations (42), (43), and (44) using Cramer's rule, we find that the determinant $D(s)$ which occurs in

the denominator is

$$D(s) = \begin{vmatrix} 1 & -e^{-sT} & 0 \\ \frac{K}{2} & \frac{K}{2} & -(K + sR_e) \\ \left(\frac{K}{2} + \frac{sR_p}{2} - 1\right) & \left(1 + \frac{K}{2} + \frac{sR_p}{2}\right) & -K \end{vmatrix}, \tag{45}$$

or

$$D(s) = -\frac{K^2}{2} + (K + sR_e)\left(\frac{K}{2} + \frac{sR_p}{2} - 1\right) e^{-sT} - \frac{K^2}{2} e^{-sT} + (K + sR_e)\left(\frac{K}{2} + \frac{sR_p}{2} + 1\right). \tag{46}$$

Since u_1, u_2, and v are bounded, on physical grounds, $D(s)$ cannot have any roots with positive real parts. The origin, of course, is a zero, as one sees by inspection. This gives rise to the constant term in the inverse transforms.

An investigation of the precise location of the roots of $D(s)$ would provide valuable information concerning the asymptotic behavior of the functions u_1, u_2, and v. We conjecture that the root, other than the origin, which lies closest to the imaginary axis in the s-plane lies on the negative real axis. If this is so, then the functions u_1, u_2, and v have the form $a_1 - a_2 e^{-a_3 t}$, for $t \to \infty$, where a_3 is the root, and a_1 and a_2 are the residues at zero and a_3 respectively. Experimentally these constants could be determined by recording the concentrations as functions of time and then selecting the constants to provide the best fit to the experimental curves.

The location of the least negative root of $D(s)$ can easily be accomplished graphically. Equation (46) can be rewritten as

$$e^{sT} = \frac{-\frac{s^2}{2} R_e R_p + s\left(R_e - \frac{KR_p}{2} - \frac{KR_e}{2}\right) + K}{\frac{s^2}{2} R_e R_p + s\left(R_e + \frac{R_e K}{2} + \frac{R_p K}{2}\right) + K}, \tag{47}$$

so that it is merely necessary to graph the exponential curve of the left-hand side and the rational function of the right-hand side and find their intersection points. One lies at $s = 0$, and the other is

negative, as an investigation of the roots of the polynomials in the numerator and denominator of the fraction in equation (47) shows. It can also be seen that an increase in T decreases the rate at which equilibrium is approached, which is physically quite reasonable.

The location of the roots of exponential polynomials such as occurs in equation (46) has been the object of many investigations (Ansoff and Krumhansl, 1948; Collatz, 1947; Hayes, 1950; Lax, 1948). In particular, we should like to call attention to the results of Pontrjagin (1942), which are described by R. Bellman and J. M. Danskin (1954) and are available in translation (Pontrjagin, 1955).

11. *Numerical aspects.* The system of equations (31) to (35) lends itself well to solution using a high-speed digital computer. The function u is known on the interval $[0, \tau]$, and v and w can be determined on this interval using the differential equations (32) and (33) along with the initial conditions of equation (35). Then equation (31) yields $u(t)$ for $\tau \leq t \leq 2\tau$, and so on. Having the time lag present increases the size of the computer memory required, but is otherwise innocuous. For more realistic models, this increased demand for memory space could become important.

12. *A model for intracellular penetration.* As was stated earlier, we wish to consider the case in which the drug enters the cells themselves and there reacts chemically with substances within the cells to form new compounds. In general, these reactions may be reversible. The situation which we wish to discuss is shown diagramatically in Figure 4.

The function $u(x, t)$ is the concentration of the drug in the capillary at position x at the time t. The functions $v(t)$ and $w(t)$ represent the spatially homogeneous concentrations of the drug in the extracellular and intracellular spaces, respectively, and $z(t)$ is the concentration of the compound ED which is formed from the chemi-

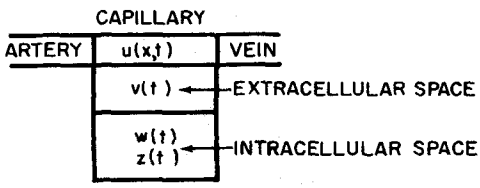

FIGURE 4. An intracellular penetration schematic.

cal union of the enzyme E and the drug D. We assume that both the enzyme E and the compound ED do not diffuse out of the intracellular space. We do wish to include the possibility that there is an active transport process which tends to concentrate the drug intracellularly. The transport term is assumed to be linear in the extracellular concentration. This is only a fair approximation even for low concentrations for the amino acid transport system (Heinz, 1954; Jacquez, 1957). It is used for the time being to demonstrate the effect of an active transport term.

The equations for this model become

$$\frac{R_p}{l} u_t = - cu_x + \frac{kA_e}{l} (v - u), \tag{48}$$

$$R_e \dot{v} = \frac{kA_e}{l} \int_0^l u(x, t)dx - kA_e v(t) - mA_i(v - w) - nA_i v, \tag{49}$$

$$R_i \dot{w} = mA_i(v - w) + nA_i v + k_2 R_i z - k_1 R_i w \, [E_0 - z], \tag{50}$$

$$\dot{z} = k_1 w \, [E_0 - z] - k_2 z. \tag{51}$$

Equation (48) has been met before. In the next equation, the last two terms measure the rate of decrease of v as a result of both diffusion and transport into the intracellular space. The last two terms in equation (50) measure the rate of increase of the concentration of the drug in the intracellular space as a result of the decomposition

$$ED \xrightarrow{k_2} D + E, \tag{52}$$

and as a result of the reaction

$$E + D \xrightarrow{k_1} ED. \tag{53}$$

In these equations, z is the concentration of the compound ED. Following the idea of Section 9, a simplified version of this problem could be considered.

13. *Discussion.* The mathematical equations obtained from the model of drug distribution in a one-organ entity present obvious analytical difficulties. As will be shown in our next paper, these are multiplied many-fold when one attempts to link a number of such models via a circulatory system to give a model of a many-

organ entity. It is to be expected that modern computational techniques will help clarify the nature of the solution to such systems.

However, the purpose of such an enterprise is more than to obtain an explicit mathematical solution of a model. As with all theorizing, it represents an attempt to gain understanding of a complex process. With this added insight, we then *return to experimentation*, and test various hypotheses. The results of this testing enable us to build more complex models, leading to further experimentation. We thus have a complex feedback process.

The very act of setting up a mathematical model points the way to experiments, to the need to measure the parameters which appear in the equations: in this case, the blood flow and blood volume of an organ, the capillary permeability and area for diffusion in an organ, and the permeabilities of various cell types. Thus even the formulation of a model which is a crude approximation to reality may be useful because it provides a well defined basepoint from which to strike out in search of new hypotheses and designs of experiments.

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