increased resistance of hemolysin production after a large intraperitoneal sheep cell dose.

Summary. 1. Splenectomy, performed one day after an intraperitoneal injection of a large dose of sheep erythrocytes, reduced the initial part of the hemolysin response, but did not significantly affect a later part. 2. The antibody-reducing effect of cortisone was significantly greater in splenectomized than in sham operated rats.

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Simplified Method for Calculating Flow, Mean Circulation Time and Downslope from Indicator-Dilution Curves. (22341)

LAWRENCE S. LILIENFIELD* AND RENATO D. KOVACH.† (Introduced by J. C. Rose.)

Cardiovascular Research Laboratory, Georgetown University Medical Center, Washington, D.C.

The use of indicator-dilution curves to measure cardiac output and "central blood volume" is widespread and of proved value (1-4). When the curves are markedly prolonged, as in heart failure, the calculations as ordinarily performed are time consuming because of the necessary integrations of the curves. Two methods of integration of the curves are in general use. The first consists of arithmetic summation of all concentrations each second from appearance time to some time later—usually through one or two cycles of semi-logarithmic paper. The second method involves replotting the curves (after extrapolation on semi-logarithmic paper) on linear paper and integrating planimetrically. The calculation of mean circulation time is done by finding the center of gravity of the linearly plotted curve on cardboard(2), or else by summing arithmetically all the products of time and concentration from the semi-logarithmic plots and dividing by the arithmetic or planimetric integration. Lewis(5), described an ingenious method of calculating the cardiac output from indicator-dilution data which eliminated the necessity for plotting the curves. Though generally useful, this method does not permit calculation of mean circulation time. In addition errors in samples which might become apparent from plots of the data could be missed more easily.

This paper proposes a method for accurately obtaining the integral, slope and mean circulation time of an indicator-dilution curve in a short time, with relatively simple calculations. The method involves a combination of arithmetic integration (summing of concentration) of a small portion of the curve, and mathematical integration of the remainder.

Method. Semilogarithmically plotted indicator-dilution curves generally can be divided into two portions. The first is the rapidly rising upslope and the curved portion of the downslope; the second is the linear portion of the downslope, extrapolated toward infinite time. It becomes apparent that the integral of the total curve is the sum of 2 areas—the area from appearance time to beginning of linearity of the downslope, and the area from the beginning of the downslope to infinite time (Fig. 1). The area of the first portion can easily be obtained by summation. Because of the steep rise and relative sharp-

* Helen H. Millenson fellow in Cardiology Research.

† Fellow, Life Insurance Medical Research Fund.

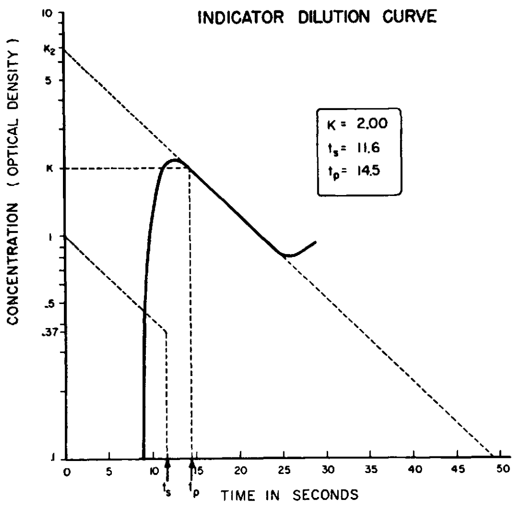

FIG. 1. Sample indicator dilution curve analyzed according to method described. (See text for symbols.)

ness of the peak only a few concentrations have to be summed—the integration of the linear portion can be determined graphically as follows, and can be added to the first integral to obtain the total area of the curve: 1. A line perpendicular to the time axis is drawn through the highest concentration on the linear downslope. The intercept of this line with the baseline is noted and recorded as t_p. 2. A line parallel to the downslope is then constructed passing through the value 1.0 of the concentration axis. Another perpendicular to the time axis is dropped from the intersection of this line with the 0.37 concentration line. The intercept of this perpendicular with the time axis is then noted and recorded as t_s. This value is the reciprocal of the downslope S and when multiplied by the flow would give the "lung" volume of Newman(4). 3. A fourth line is now drawn parallel to the time axis through the beginning of the linear downslope. The point at which this line crosses the concentration axis is noted and recorded as K. 4. The product Kt_s is equal to the integral of the straight line portion of the curve. As stated previously this integral is added to the arithmetically obtained integral of the first portion of the curve to obtain the total area. The amount of indicator injected into the circulation is divided by the total integral to obtain flow.

To calculate the mean circulation time of the entire curve we proceed as follows: 1. The product Kt_s $(t_s + t_p)$ is obtained. 2. The concentration for each second, from appearance of indicator to beginning of linear downslope, is obtained from the curve and multiplied by its respective time. These products are summed. 3. This sum is added to the value obtained from step 1. above. 4. The final sum (from 3. above) is divided by the previously obtained total area of the curve. The result is the mean circulation time, T_m. The validity of the method is apparent from examination of the mathematical derivation in the appendix.

Summary. 1. A new graphical method for calculating flow, downslope and mean circulation time from semilogarithmic plots of indicator-dilution concentration-time curves is described. 2. The advantages of employing this method of calculation include speed and accuracy.

APPENDIX: *Mathematical Proof of Method.*

I. Slope determination of indicator dilution curves. The slope is usually obtained from formula

$$(1)\quad \text{Slope } S = \frac{\log_e C_2 - \log_e C_1}{T_2 - T_1}$$

This formula is applicable with any values of C_2 and C_1 obtained from the downslope. Since the slope of any line parallel to the downslope is the same as the downslope we can construct a line parallel to the downslope passing through the 1.0 concentration value. Slope of this line would be identical with slope of our original. We can choose any 2 values of C_2 and C_1 to determine the slope. Choosing values $C_1 = 1.0$ and $C_2 = 0.37 = e^{-1}$, the corresponding times for these concentration values would be T_1 and T_2. Since our line intersects the concentration axis at 1.0 at time 0 then $T_1 = 0$. Substituting into our formula (1) we obtain

$$(2)\quad \text{Slope } S = \frac{\log_e C_2 - \log_e 1.0}{T_2 - 0}$$

Since $\log_e 1.0 = 0$ then

$$(3)\quad S = \frac{\log_e C_2}{T_2}$$

Since we have set $C_2 = e^{-1}$ we now substitute this and get

$$(4)\quad S = \frac{\log_e e^{-1}}{T_2}$$

Since $\log_e e^{-1} = -1$ then

$$(5)\quad S = \frac{-1}{T_2} \quad \text{or}$$

(6) $T_2 = \frac{-1}{S}$, the minus sign indicating the direction of the slope.

Thus time T_2 (the time corresponding to a C_2 of 0.37) is equal to reciprocal of the downslope.

II. Flow determination

Total area of the curve can be represented by the integral $\int_0^{\infty} Cdt$. By drawing a line perpendicular to the time axis through highest portion of the linear downslope, curve can be divided into 2 portions whose total area is the sum of the area up to the perpendicular line and the area from the perpendicular to infinite time. Expressed mathematically:

$$\int_0^{\infty} Cdt = \int_0^{t_p} Cdt + \int_{t_p}^{\infty} Cdt$$

Value of the integral $\int_0^{t_p} Cdt$ is obtained arithmetically by summation.

The value of the integral $\int_{t_p}^{\infty} Cdt$ can be shown to be K/S as follows:

If a line parallel to the downslope is drawn through the concentration axis at K, (highest value of linear downslope) then the area under this line must be equal to area under downslope since both triangular areas (on semilogarithmic paper) are congruent and at the same concentration level. The equation representing this constructed line is

$$(7)\quad C = Ke^{-St}$$

its area is

$$(8)\quad \text{Area} = \int_0^{\infty} Ke^{-St}dt = \text{area under downslope} = \int_{t_p}^{\infty} Cdt$$

Since K is constant we can write

$$(9)\quad \int_{t_p}^{\infty} Cdt = K \int_0^{\infty} e^{-St}dt$$

Integrating the right hand expression we get

$$(10)\quad \int_0^{\infty} Cdt = K\left[\frac{-1}{S} e^{-St}\right]_0^{\infty} = K/S$$

By adding this area K/S to the arithmetically obtained value of $\int_0^{t_p} Cdt$, we obtain the value of the total integral to infinite time. By dividing the amount of indicator injected, Q, by this integral the flow results from the formula

$$(11)\quad \text{Flow} = \frac{Q}{\int_0^{\infty} Cdt}$$

III. Mean circulation time determination. The mean circulation time is defined as

$$(12)\quad T_m = \frac{\int_0^{\infty} Ctdt}{\int_0^{\infty} Cdt}$$

Value of denominator is determined as described above. Value of numerator is derived as follows:

The integral $\int_0^{\infty} Ctdt$ can be divided into 2 parts (by a line drawn through the highest point on the downslope perpendicular to the time axis) so that

$$(13)\quad \int_0^{\infty} Ctdt = \int_0^{t_p} Ctdt + \int_{t_p}^{\infty} Ctdt$$

Value of $\int_0^{t_p} Ctdt$ is obtained arithmetically by summing all the products of concentrations and time each second up to t_p. To this sum is added value of integral $\int_{t_p}^{\infty} \text{Ctdt}$ determined as follows:

Since the curve of concentrations against time plotted semilogarithmically is a straight line from t_p to infinity this curve can be expressed by the formula

$$(14)\quad C = K_2 e^{-St}$$

where K_2 is the intercept of this line extrapolated back to the concentration axis (zero time).

Substituting (14) into the integral we are trying to determine we can say

$$(15)\quad \int_{t_p}^{\infty} \text{Ctdt} = \int_{t_p}^{\infty} tK_2e^{-St}dt$$

Since K_2 is a constant we can write

$$(16)\quad \int_{t_p}^{\infty} \text{Ctdt} = K_2 \int_{t_p}^{\infty} te^{-St}dt$$

Solving we get

$$(17)\quad \int_{t_p}^{\infty} \text{Ctdt} = K_2\left[\frac{e^{-St}}{(-S)^2}(-St-1)\right]_{t_p}^{\infty}$$

$$= \frac{K_2e^{-St_p}}{S^2}(St_p + 1)$$

The expression can be simplified as follows:

The area under the downslope from t_p to infinity is equal to the area under the curve obtained by drawing a parallel line through the concentration axis (zero time) at K. Equating these areas we get

$$(18)\quad \int_{t_p}^{\infty} K_2e^{-St} = \int_{0}^{\infty} Ke^{-St}$$

and solving

$$(19)\quad \frac{K_2 e^{-St_p}}{S} = \frac{K}{S}$$

or

$$(20)\quad K_2 = \frac{K}{e^{-St_p}}$$

substituting the value for K_2 from (20) into equation (17) we get

$$(21)\quad \int_{t_p}^{\infty} \text{Ctdt} = \frac{K}{S^2}(1 + St_p) = \frac{K}{S}\frac{1}{S}(1 + St_p)$$

$$\text{Since } \frac{1}{S} = t_s$$

$$(22)\quad \int_{t_p}^{\infty} \text{Ctdt} = Kt_s\,(t_s + t_p)$$

Adding this to the arithmetically obtained value for $\int_{0}^{t_p} \text{Ctdt}$ we get the entire value for $\int_{0}^{\infty} \text{Ctdt}$ which when substituted into equation (12) gives mean circulation time.

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