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KINETICS OF DISTRIBUTION OF SUBSTANCES ADMINISTERED TO THE BODY

II. The Intravascular Modes of Administration

BY

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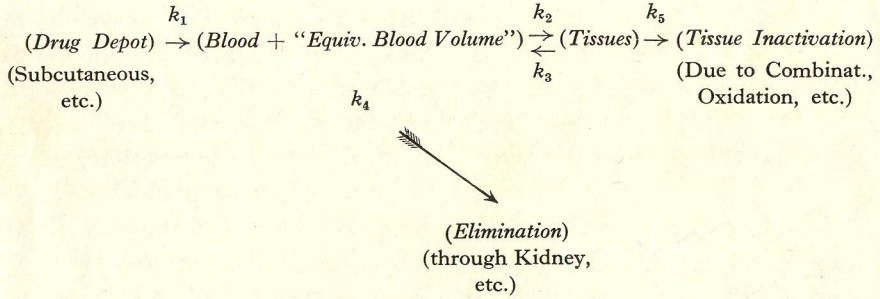
INTRODUCTION

In a preceding paper [TEORELL (1)] theoretical treatment has been given for the kinetics of drug distribution common for the *per os*, *subcutaneous* and several other modes of administration. The equations derived were all based upon the assumption that the passage of a drug across the tissue boundaries obeyed FICK's law for molecular diffusion. The scheme of distribution was the following, the arrows indicating a passage process, mathematically equivalent to a molecular diffusion course :



The " $k : s$ " are velocity constants for each of the processes shown, they are defined in the preceding communication.

In this paper the intraveneous modes of application will be theoretically treated as limiting cases of the formulas already developed. The intraveneous administration may be given as (*a*) " prompt " injection, i.e., the whole dose is given at once, as (*b*) " intermittent " injections, when the dose is given in smaller portions over a longer period, or as

(*c*) " drop " injections or " continuous " injection (German : " Dauer-Injection "). At present we omit the intermittent mode, because generally treated it will give too cumbersome calculations.

For the *simplified* case where the blood and tissue spaces can be regarded as a kinetical unit, formulas for the drop injection have already been derived by WIDMARK, WIDMARK and TANDBERG (2) and TEORELL (3). WIDMARK and TANDBERG have presented an equation for the intermittent case. Similar attempts in regard to the *general*, " prompt " injection have been made by DOMINGUEZ (4) and collaborators. Although his resulting equations have the correct form, the constants employed are meaningless because the fundamental assumption from which the formulas are derived, is not correct, as was already pointed out in the previous paper on p. 218 [TEORELL (1)]. Furthermore, the drug inactivation in the tissues was not considered by DOMINGUEZ et al.

1. " PROMPT " INTRAVENEOUS INJECTION

If we consider a subcutaneous injection and imagine that the rate of resorption from the depot to the blood is very large, the effect is the same as if the dose had been injected directly into the blood. Accordingly the prompt intraveneous injection can be regarded as a limiting case of a subcutaneous injection and the formulas, Eq. 11 etc., already derived, can be used together with their auxillary equations [TEORELL (1)], providing the value of the " resorption " constant is put equal to infinity ($k_1 = \infty$). Some difficulties will arise at first, because several indeterminate expressions appear which must be evaluated before the new formulas can be written. Since these evaluations are only mathematical routine (1), they will be omitted here. The limiting values of the constants C_1, C_2, R_1 and R_2, employed in the previous equations, will become

$$\lim_{k_1 \to \infty} C_1 = -\frac{k_2 + k_4 + m_2}{m_1 - m_2} . N_o = E_1 . N_o \qquad (1)$$

$$\lim_{k_1 \to \infty} C_2 = \frac{k_2 + k_4 + m_1}{m_1 - m_2} . N_o = E_2 . N_o \qquad (2)$$

$$\lim_{k_1 \to \infty} R_1 = \frac{k_2}{m_1 - m_2} . N_o \qquad (3)$$

$$\lim_{k_1 \to \infty} R_2 = -\frac{k_2}{m_1 - m_2} . N_o \qquad (4)$$

(1) Cf. MELLOR (5), p. 304.

Inserting these values in the equations of the previous paper and observing that the exponentials containing k_1 vanish, the following equations, valid for the *prompt intraveneous* injection, are obtained :

$$\textit{Blood Amount, } y = N_o(E_1 \cdot e^{m_1 t} + E_2 \cdot e^{m_2 t}) \tag{5}$$

$$\textit{Tissue Amount, } z = \frac{k_2}{m_1 - m_2} N_o(e^{m_1 t} - e^{m_2 t}) \tag{6}$$

$$\textit{Eliminated Amount, } u = -k_4 N_o \left[\frac{E_1}{m_1}(1 - e^{m_1 t}) + \frac{E_2}{m_2}(1 - e^{m_2 t})\right] \tag{7}$$

$$\textit{Inactivated Amount, } w = \frac{k_2 k_5}{m_1 - m_2} N_o\left[\frac{1}{m_2}(1 - e^{m_2 t}) - \frac{1}{m_1}(1 - e^{m_1 t})\right] \tag{8}$$

Here E_1, E_2 have the significance denoted in Eqs. 1 and 2. The other constants have the same meaning as defined in the previous general paper, or

k_2, k_3, k_4 and k_5 are the velocity constants

$$m_1 = -0.5p + \sqrt{0.25p^2 - q} \tag{9}$$

$$m_2 = -0.5p - \sqrt{0.25p^2 - q} \tag{10}$$

$$p = k_2 + k_3 + k_4 + k_5 \tag{11}$$

$$q = k_2 k_5 + k_3 k_4 + k_4 k_5 \tag{12}$$

Of course, these formulas can be derived directly from the fundamental differential equations, if these are subjected to appropriate modifications.

Some Approximation Formulas.—a) In the case where the intensity of tissue take-up and inactivation can be neglected compared with the kidney elimination (velocity constant k_4), the blood amount formula, Eq. 5, reduces to

$$y \approx N_o . e^{-k_4 t} \tag{5a}$$

The same equation may be applied when the substance exchange between blood and tissue (volume V_2 and V_3 respectively) is so rapid, that these volumes can be taken together as a mathematical unit. In such a case the elimination constant should be the fraction $V_2 : (V_2 + V_3)$ of the k_4 used in Eq. (5*a*).

b) A similar formula will be approximately valid in the case of a tissue take-up (velocity constant k_2) with an intensive inactivation keeping the tissue drug concentration very low, providing the elimination is neglectable (1).

$$y \approx N_o . e^{-k_2 t} \tag{5b}$$

Graphical Representation of the Equations.—The FIG. 1 is a diagram obtained from Eqs. 5-8; this may very well correspond to an actual

(1) It should be pointed out here, that caution sometimes is necessary in the derivation of special cases of the general expressions (Eqs. 5-8), because the limiting values (Eqs. 1-4) have been derived under the assumption that the only constant that could have an extreme value equal to 0 or ∞ was k_1, the resorption constant; it was put equal to infinity.

case. The velocity constants are chosen as an indicated in the legend of the figure. By a comparison of this diagram with FIG. 2 in a preceding paper [TEORELL (1), p. 217] it becomes evident, that there is not much difference between the curves of a rapidly resorbed, say, subcutaneous administration and an intraveneous injection with exception of the very first period with the ascending curves, i.e. the "resorptive period." The relations between the blood and tissue concentration curves have already been discussed in connection with a criticism of DOMINGUEZ's results [TEORELL (1), p. 218].

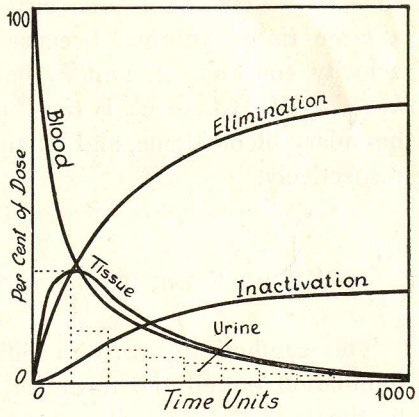


FIG. 1

Typical Case of Intraveneous Injection. Dotted bars indicate output in urine samples taken at equidistant intervals. ($k_2 = 0.01$; $k_3 = 0.01$ [$V_2 : V_3 = 1 : 1$]; $k_4 = 0.005$; $k_5 = 0.002$).

The Tissue Concentration Curves and the factors having influence upon them would perhaps be more important to discuss than the blood curves, because a great many drug effects are displayed in the tissues. The course of the tissue curves can, in a general way, be best characterized in terms of the position of the maximum in regard to its time and the height of this maximum.

For this purpose we evaluate the maximum conditions of Eq. 6. By differentiating with respect to time, t, and equating the derivative to zero and solving in an appropriate way for the t-maximum and z-maximum, we finally obtain

$$t_{max.} = \frac{2.3}{m_1 - m_2} \log \frac{m_2}{m_1} \tag{6a}$$

$$z_{max.} = N_o \cdot \frac{k_2}{(-m_2)} \left[\frac{m_2}{m_1}\right]^{\frac{m_1}{m_1 - m_2}} \tag{6b}$$

The influence of a variation of any of the velocity constants, which are the constituents of m_1 and m_2, is difficult to overlook. Two conclusions can, however, be read off directly :

a) *The time for the appearance of the concentration maximum in the tissues is independent of the dose injected;*

b) *The height of this maximum is directly proportional to the amount injected* (N_o).

By appropriate considerations, which are omitted here, it can be shown, that *the slower the tissue take-up, the lower the concentration maximum in the tissue becomes and the later this maximum appears.* A slow tissue take-up is due either to a decreased permeability, or to a large tissue volume, because it should be remembered that the velocity constants k_2 and k_3 have been defined as $k_2 = k_2'/V_2$ and $k_3 = k_2'/V_3$, where k'_2 is the " permeability coefficient," valid for the boundary blood-tissue, and V_2 and V_3 are the blood and tissue volume respectively.

2. " Drop " injection (continuous intraveneous injection)

The symbolically written differential equations which lie at the foundation of all the formulas here presented were (numbers refer to those of the preceding paper) :

$$[D + (k_2 + k_4)]y - k_3 z = k_1 . N_o . e^{-k_1 t} \qquad (I : 7a)$$

$$- k_2 y + [D + (k_3 + k_5)]z = 0 \qquad (I : 9a)$$

The right member $k_1 . N_o . e^{-k_1 t}$ denotes the rate of passage, $-\frac{dx}{dt}$, from a depot into the blood and changes evidently with time. When applying a continuous intraveneous administration, the *rate* of passage of the substance into the blood is constant and independent of time. Accordingly in Eq. I : 7*a* we can substitute for $k_1 . N_o . e^{-k_1 t}$ the constant *rate of injection*, denoted by r, the rest of the system remaining unchanged, and we have directly a means of derivation for the formulas of the drop injection case. The mathematical solutions are of the same character as before, and being a matter of a routine work they will be omitted here. The final results can be written :

$$\text{Blood Amount, } y = r . [A_1 . e^{m_1 t} + A_2 . e^{m_2 t} + I] \qquad (13)$$

$$\text{Tissue Amount, } z = r . [B_1 . e^{m_1 t} + B_2 . e^{m_2 t} + J] \qquad (14)$$

$$\text{Eliminated Amount, } u = k_4 . r\left[I . t - \frac{A_1}{m_1}(1 - e^{m_1 t}) - \frac{A_2}{m_2}(1 - e^{m_2 t}) \right] \qquad (15)$$

$$\text{Inactivated Amount, } w = k_5 . r\left[J . t - \frac{B_1}{m_1}(1 - e^{m_1 t}) - \frac{B_2}{m_2}(1 - e^{m_2 t}) \right] \qquad (16)$$

The following abbreviations are used :

$$A_1 = \frac{q + m_2(k_3 + k_5)}{q(m_1 - m_2)} \qquad (17)$$

$$A_2 = -\frac{q + m_1(k_3 + k_5)}{q(m_1 - m_2)} \qquad (18)$$

$$B_1 = \frac{k_2 m_2}{q(m_1 - m_2)} \quad \text{and} \quad B_2 = -\frac{k_2 m_2}{q(m_1 - m_2)} \qquad (19a, 19b)$$

$$I = \frac{k_3 + k_5}{q} \qquad (20)$$

$$J = \frac{k_2}{q} \qquad (21)$$

Here m_1, m_2, p, q and the velocity constants, the $k : s$, keep their previous significance (cf. p. 228).

Graphical Representation of the Equations and Conclusions.—The Fig. 2 is an illustration of a postulated case of drop injection, where both kidney elimination and tissue inactivation are assumed to be appreciable. We notice that both the blood and the tissue amount soon approaches a constant value. From Eqs. 13 and 14 it is immedialy seen that *the substance amount present in the blood and the tissues respectively are, at any given instant, directly proportional to the rate of injection* (r).

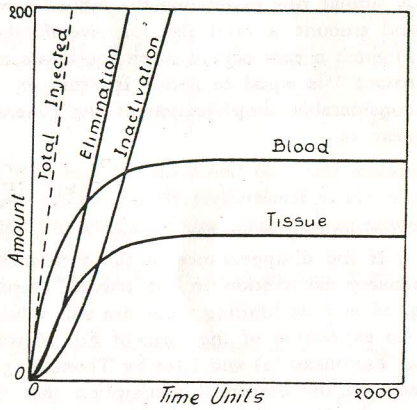


Fig. 2

Typical Case of Drop Injection. ($r = 1$; $k_2 = 0{,}01$; $k_3 = 0.01$ i.e. $[V_2/V_3 = 1 : 1]$; $k_4 = 0.005$; $k_5 = 0.005$).

The heights of the constant values, finally approached, are derived by putting time $t = \infty$, when Eqs. 13 and 14 respectively reduce to :

$$y_\infty = r . \frac{k_3 + k_5}{q} \qquad (22)$$

$$z_\infty = r . \frac{k_5}{q} \qquad (23)$$

For further special cases of y and z values, see p. 232.

In regard to the *amount eliminated* through kidneys etc. u, and the *amount inactivated* in the tissues, w, Fig. 2 shows, that in the beginning there is a very slow elimination and inactivation, but, as is natural, they rapidly increase later and finally approach a straight line course, indicating that *after a sufficiently long time there is a constant rate of elimination and inactivation.*

Some Special Cases.—a) If we assume that $k_5 = 0$ in the general formulas Esq. 13 and 14, i.e. in the absence of any tissue inactivation, these equations will appear as

$$y_{k_5=0} = \frac{r}{k_2}\left(\frac{k_4 + m_2}{m_1 - m_2} e^{m_1 t} - \frac{k_4 + m_1}{m_1 - m_2} e^{m_2 t} + 1 \right) \qquad (24)$$

$$z_{k_5=o} = \frac{k_2}{k_3 k_4} r\left(\frac{m_2}{m_1 - m_2} e^{m_1 t} - \frac{m_1}{m_1 - m_2} e^{m_2 t} + 1\right) \qquad (25)$$

If time is put equal to infinity, i.e. $t = \infty$, we get as limiting cases

$$y_{\infty, k_5=o} = \frac{r}{k_4} \quad \text{and} \quad z_{\infty, k_5=o} = \frac{k_2 \cdot r}{k_3 \cdot k_4} \qquad (24a,\ 25a)$$

Remembering that $k_2 : k_3 = V_3 : V_2$ [tissue and blood volume, cf. TEORELL (1), FIG. 1], we can now state that *after a sufficiently long time the drug concentrations* (1) *in the blood and in the tissues both are identical and have a value directly proportional to the injection rate* (r) *and inversely proportional to the elimination intensity* (k_4).

A similar rule expressing the influence of r and k_4 upon the maximum value of the blood amount is valid also for several other special cases :

b) Such a case occurs when the tissue take-up is neglectable. Here the " take-up constant " is equal to zero. Inserting $k_2 = 0$ in the auxillary Eqs. 17-21 leads to a considerable simplification of the general blood amount formula, Eq. 13; it will appear as

$$y_{k_2=o} = \frac{r}{k_4}(1 - e^{-k_4 t}) \qquad (26)$$

The limiting value for y when $t = \infty$, is again $r : k_4$.

c) If the disappearance of the substance from the blood is mainly caused by an intensive inactivation in the tissues, keeping the concentration there close to zero, Eq. 26 and its limiting value are still valid, but k_4 should be substituted by k_2.

An expression of the form of Eq. 26 was developed already in 1925 by WIDMARK and TANDBERG (2) and later by TEORELL (3). On both occasions the derivations were made on the empirical assumption that the " rate of disappearance " was directly proportional to the blood concentration present.

d) When the inactivation intensity is *moderate*, but in the *absence* of any considerable *elimination*, the general Eqs. 13 and 14 must be used. Their limiting values at $t = \infty$ when $k_4 = 0$ become

$$y_{\infty, k_4=o} = \frac{k_3 + k_5}{k_2 k_5} \cdot r \qquad (27)$$

$$z_{\infty, k_4=o} = \frac{r}{k_5} \qquad (28)$$

During such circumstances the amount (and concentration) in the tissues of the injected substance, after elapse of sufficient time, will become directly proportional to the injection rate (as always) and inversely proportional to the tissue inactivation intensity (for the blood conditions, Eq. 27, the rule is not easily expressed in a few words).

e) A simple equation analogous to Eq. 26 and a rule as presented under *a*) will be valid also for such a case, when the substance exchange between the blood and the tissue is so rapid that these two anatomical spaces can be taken together as a kinetical unit. The significance of k_4 will be the fraction $V_2 : (V_2 + V_3)$ of its original value (V_2 and V_3 are the blood and tissue volumes respectively).

f) If it should happen that neither the kidney elimination nor the tissue inactivation is active, no constant value will be approached by the blood or the tissue concentration of the injected substance; instead there will be a continous growth of both the concentrations. During these conditions the velocity constants k_4 and k_5 are equal to zero. Under *a*) above, the case $k_5 = 0$ was already considered, resulting in the Eqs. 24 and

(1) Concentration $= \frac{\text{amount}}{\text{volume}}$, or $\frac{y}{V_2}$ and $\frac{z}{V_3}$ is blood concentration and tissue concentration respectively.

25. By putting k_4 also equal to zero in the general Eqs. 13 and 14, these expressions will appear in indeterminate forms, which must be separately evaluated. The solutions for these particular equations will become somewhat tedious. An alternative, shorter procedure consists in starting with new fundamental equations and then solving. These new equations are :

$$\begin{cases} \frac{dy}{dt} = r + k_3 z - k_2 y & (29) \\ r \cdot t = y + z & (30) \end{cases}$$

The physical meaning of the Eqs. 29 and 30 is obvious and needs no further explanation. Both procedures lead, of course, to identical results which are written :

$$y_{k_4=k_5=o} = \frac{r}{h}\left[k_3 t + \frac{k_2}{h}(1 - e^{-ht})\right] \qquad (31)$$

$$z_{k_4=k_5=o} = \frac{r}{h}\left[k_2 t - \frac{k_2}{h}(1 - e^{-ht})\right] \qquad (32)$$

Here h stands for $(k_2 + k_3)$. We notice that *both the blood and the tissue amount of the substance*, y *and* z, *at any fixed time, are always directly proportional to the rate of injection* (r), which was to be expected, since this statement was made in connection with the general Eqs. 13 and 14 on p. 231.

The differentiation of y and z in the Eqs. 31 and 32 with respect to time t, gives immediately

$$\frac{dy}{dt} = \frac{k_3 \cdot r}{h} + \frac{k_2 \cdot r}{h} e^{-ht} \qquad (33)$$

$$\frac{dz}{dt} = \frac{k_2 \cdot r}{h} - \frac{k_2 \cdot r}{h} e^{-ht} \qquad (34)$$

At the very beginning of the injection we get (by putting $t = 0$),

$$\frac{dy}{dt} = r \quad (\text{when } t = 0) \qquad (33a)$$

$$\frac{dz}{dt} = 0 \quad (\text{when } t = 0) \qquad (34a)$$

and for the later stages, when time could practically be put equal to infinity,

$$\frac{dy}{dt} = \frac{k_3}{k_2 + k_3} \cdot r \ (\text{when } t = \infty) \qquad (33b)$$

$$\frac{dz}{dt} = \frac{k_2}{k_2 + k_3} \cdot r \ (\text{when } t = \infty) \qquad (34b)$$

As the ratio $k_2 : k_3$ is equal to $V_3 : V_2$, we realize that *the rate of concentration change*, $\frac{1}{V_2}\frac{dy}{dt}$ and $\frac{1}{V_3}\frac{dz}{dt}$, in the blood and the tissues respectively will become the same when sufficient time has elapsed; however, during the earlier stage following the commencement of the injection, a very marked difference is to be expected according to Eqs. 33*a* and 34*a*. These conclusions are clearly demonstrated by FIG. 3.

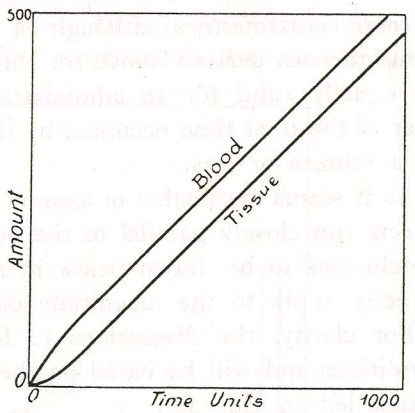


FIG. 3

A Special Case of Drop Injection, here elimination and tissue inactivation both are absent.

($r = 1$; $k_2 = 0.01$; $k_3 = 0.01$ i.e. $V_2/V_3 = 1 : 1$; $k_4 = 0$; $k_5 = 0$).

3. Possible bearings upon the pharmacological effects of rapidly disappearing substances

In connection with the discussion of the continuous intraveneous injection some simple quantitative relations have been pointed out between blood or tissue amount of a drug injected, the rate of injection and certain velocity or diffusion constants (p. 230). These constants referred to the intensity of drug disappearance from the blood circulation. For many pharmacological substances the net intensity of disappearance from the blood seems to be very high; for instance, histamine or adrenaline disappear with extreme rapidity, at least to judge from the transient effects they produce upon the blood pressure. If the velocity constants mentioned have large values, the curve courses for amount and concentration illustrated in the diagrams will occur relatively much earlier in time. Accordingly, when dealing with *rapidly* disappearing substances, it may be necessary from a kinetical point of view to treat a " prompt " injection *as being a continuous injection*, although of shorter duration. Hence, all the consequences derived above for the continuous mode injection would be equally valid for an administration made by syringe or burette, even if the total time occupied by the injection should be of the order of a minute or less.

As it seems reasonable to assume that a great many pharmacological effects run closely parallel to the drug concentration in the blood, the conclusions to be drawn below in regard to such concentrations may directly apply to the magnitude of the effects produced.

For clarity, the discussions to follow will be restricted to blood conditions and will be based on the somewhat simplified assumptions which led to Eq. 26 :

$$y = \frac{r}{k}(1 - e^{-kt}) \qquad (35)$$

Here k stands as a " disappearance constant " (instead of k_2 or k_4). Furthermore, special attention will be paid to the *maximum* value of the drug amount in the blood. This maximum value, $y_{max.}$, will obviously be attained at the end of the injection. Calling the dose injected N_o, the duration of the injection v and the rate of injection r, then r will be defined as

$$r = \frac{N_o}{v} \qquad (36)$$

The value of $y_{max.}$ can be found if t in Eq. 35 is substituted by v or its equivalent $N_o : r$ as

$$y_{max.} = \frac{r}{k}\left(1 - e^{-k.\frac{N_o}{r}}\right) \qquad (37a)$$

or equally well

$$y_{max.} = \frac{N_o}{v \,.\, k}(1 - e^{-kv}) \qquad (37b)$$

These last equations show, provided k remains constant, that the value of $y_{max.}$ may depend upon : (A) The dose injected, if r is kept constant, (B) The injection rate, if N_o is kept constant, or (C) The dose, if v is kept constant.

A. *Variation of the Dose, while Keeping the Injection Rate Constant.* In this case N_o is the only variable of the Eq. 37*a*. It can be inferred from the equation that

the maximum drug amount in the blood (or concentration) attained after the administration of increasing doses, all injected at the same rate, will become proportional to the dose given but only for relatively small doses. With further increase of the dose, a constant limiting concentration

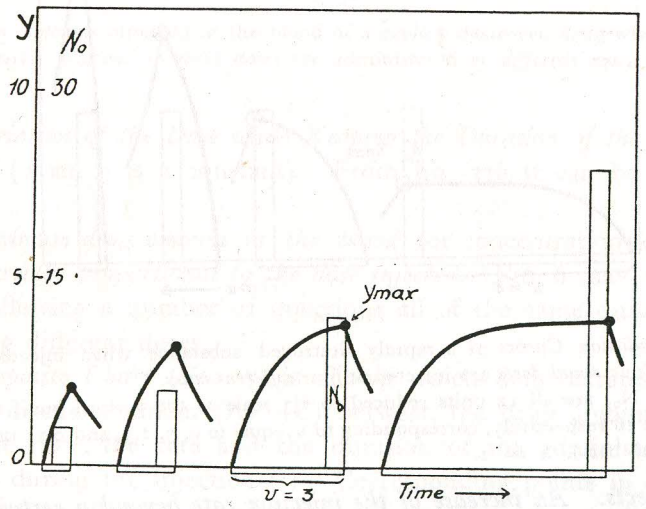


Fig. 4

Blood Cumulation Curves of a rapidly destroyed substance when injected intraveneously. Four *different doses* are all injected at the *same rates*.—The doses N_0 are 3, 6, 12 and 24 units and reduced to 1/3 scale as the vertical bars. The rate r is 4. The horisontal bars indicate the duration of the injections (v). $k = 1$. Immediately after the cessation of the injection the curves start to fall (according to the equation $y = y_{max.}e^{-k(t-v)}$).

will be approached, which never will be exceeded, even if still larger doses are tried. The possible pharmacological effects can also be expected to approach a maximum not influenced by a further increase of the dose.

The value of the limiting drug amount in the blood will be

$$y_{max.} = \frac{r}{k} \text{ (when } N_o \text{ is large)} \qquad (38)$$

These statements under (A) are schematically illustrated by FIG. 4.

B. *Variation of the Injection Rate while keeping the Dose Constant.* Now r or v is a variable of Eq. 37*a* or 37*b*. The following important conclusion can be drawn :

Depending upon the rate of injection, identical doses of a substance can produce different blood concentrations and thereby different pharmacological effects. An increase of the injection rate beyond a certain limit will not produce any appreciable augmentation of the blood drug amount (or concentration). It can easily be shown that the limiting amount approached can be written

$$\operatorname{Lim}_{r \to \infty} y_{max.} = \operatorname{Lim}_{r \to \infty} \frac{r}{k}\left(1 - e^{-k.\frac{N_0}{r}}\right) = N_o \qquad (39)$$

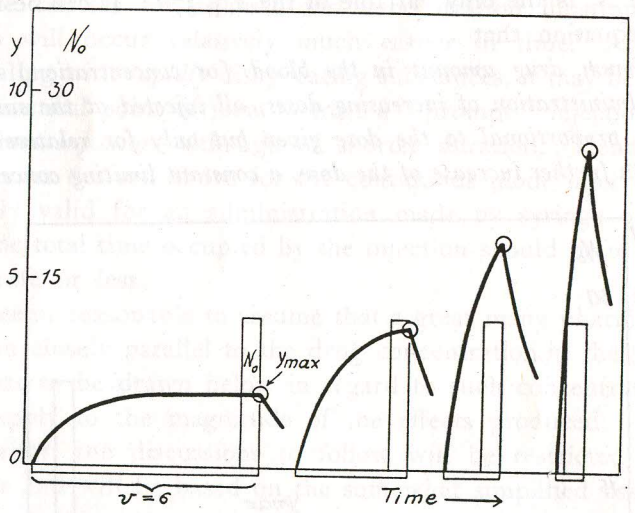


FIG. 5*a*

Blood Cumulation Curves of a rapidly destroyed substance when injected intraveneously. Four *equal doses* are injected at four *different rates*.

The doses, N_0, are all 12 units reduced to 1/3 scale as the vertical bars; the rates are 2, 4, 8 and 16 respectively, corresponding to v equal to 6, 3, 1.5, and 0.75 time units (the horisontal bars). $k = 1$.

or, in words, the blood drug amount approached at a high injection rate will become equal to the dose injected. FIG. 5*a* is intended to demonstrate these consequences. So is also FIG. 5*b* in which a whole family of curves is drawn, showing the $y_{max.}$ values at varying injection rates for a number of different doses.

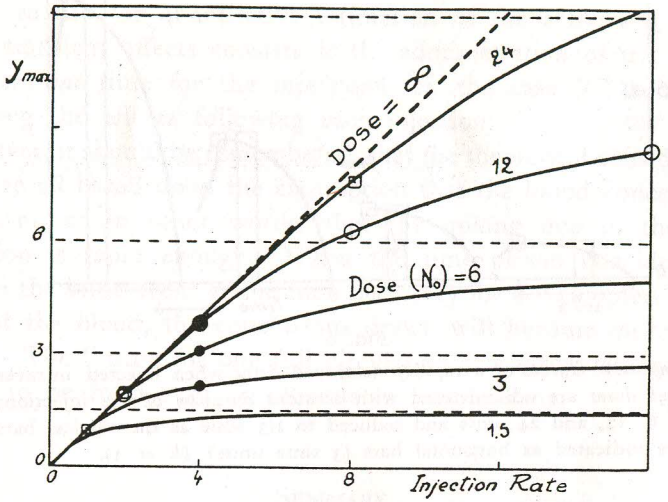


FIG. 5*b*

Maximum Amounts obtained in the blood of a rapidly destroyed drug when injected intraveneously. *Various constant doses* are administered at *different rates*. ($k = 1$).

C. *Variation of the Dose while Keeping the Duration of the Injection Constant* (when v is a constant). From Eq. 37*b* it can be read off that

the maximum drug amount in the blood (or concentration) *obtained will be directly proportional to the dose injected.* FIG. 6 may show the effects following a number of injections all of the same duration but containing different doses.

A Composite Chart (FIG. 7) is shown which demonstrates all the relations discussed under (A)—(C) between the drug amount in the blood, the dose, the rate and the duration of the administration at *any* time during the injection (1). Corresponding points in FIG. 4-7 are marked as filled or open circles, representing the conditions (A) and (B) respectively, the squares indicate the case (C). The chart

(1) The chart may also demonstrate the consequences of a variation of the "disappearing constant," because a change of k has the same effect as a corresponding change of v, cf. Eq. 37*b*.

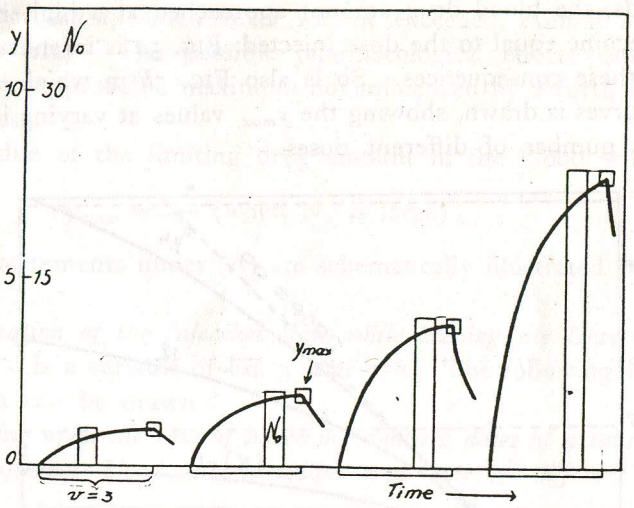


FIG. 6

Blood Cumulation Curves of a rapidly destroyed drug when injected intraveneously. Four *different doses* are administered with *constant duration* of the injections. The doses are 3, 6, 12, and 24 units and reduced to 1/3 scale as the vertical bars. The durations are indicated as horisontal bars (3 time units). ($k = 1$).

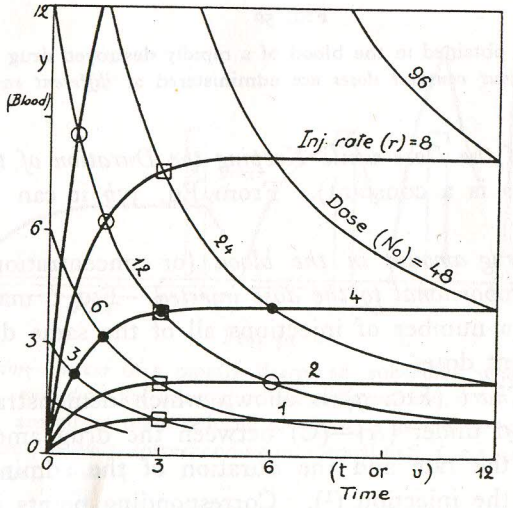


FIG. 7

A Composite Chart. The figure shows the relations between blood drug amount (y), dose injected (N_0), injection rate (r) and time (t or v). FIGURES 4-6 are special cases obtained from this diagram and the corresponding points are marked as filled or open circles and squares.

The chart is valid for a rapidly destroyed substance when injected intraveneously, and covers the time interval $t = 0$ to $t = v$ i.e. only the conditions *during* the injection. The curves are drawn according to Eq. (37*a*) or (37*b*) where the " disappearance constant," k, is put equal to 1.

is based upon the relations between the four variables as given by the equations 35, 37*a* and 37*b*.

The conditions discussed here are frequently met with in several procedures of biological essay and the results arrived at have been considered empirically by many pharmacologists. The theoretical discussions above support the experimental experience that the best method to use for quantitative estimation of the activity of a drug having transient effects consists in the administration of test samples using *constant* time for the injections [cf. the case (C) above] and comparing the effects following each injection.

However, it should be remembered, that the theoretical considerations here were all based upon the assumption that the blood concentration is uniform, or in other words, that the mixing due to the blood circulation is rapid enough. When the time period considered approaches the same order as the time necessary for a " complete circulation " of the blood, the conclusions drawn will become more or less invalid. The " time for one full circulation " is estimated by several authors to be from 7 to 20 seconds in mammalians.

SUMMARY

On the basis of a previous theoretical study, quantitative relations have been derived here, which may be valid for the distribution of substances injected intraveneously or intra-arterially.

The spreading of a substance in the body is regarded as a sequence of successive, simultaneous steps of processes, formally obeying FICK's law.

The considerations are divided into three parts : (1) the ordinary, " prompt," intraveneous injection, and (2) the continuous or " drop " injection, and (3) the kinetics of rapidly disappearing substances.

Formulas are derived for the amount of a drug present in the blood and in the tissues, and the drug amount eliminated through the kidneys, etc. and inactivated in the tissues. These amounts (or concentrations) are described as functions of time and permeability properties. The results are illustrated by several diagrams.

The influence of the various factors, involved in the formulas, upon the drug distribution are discussed, and simple rules, in appropriate cases, are advanced.

Finally, the influence of the rate of injection, and the magnitude of the dose, in regard to the pharmacological effect produced, is

discussed. It is pointed out that important consequences have to be considered, when dealing with substances, which are quickly destroyed or otherwise rapidly disappear in the body.

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LABORATOIRE DE PHYSIOLOGIE. SORBONNE, PARIS

RECHERCHES SUR LES APPAREILS ITÉRATIFS

Analyse du fonctionnement neurosécréteur de la glande sous-maxillaire

SECONDE PARTIE

Les modifications de l'excitabilité neurosécrétoire par divers types d'agents pharmacologiques

PAR

A. ET B. CHAUCHARD ET PAUL CHAUCHARD

(Travail reçu le 21-6-1937.)

Introduction

Nous avons exposé dans la première partie (1), notre technique et les caractéristiques normales de l'excitabilité neurosécrétoire : temps de sommation : 8 sec., caractéristique de la glande sous-maxillaire; chronaxie de constitution : 0,4 msec. pour la corde; 1 à 1,5 msec. pour le sympathique. Nous allons maintenant étudier les modifications de ces divers paramètres au cours de l'action de quelques agents pharmacodynamiques type, ayant une action sur la sécrétion.

De nombreux agents pharmacologiques agissent sur la sécrétion, les uns en provoquant une abondante sécrétion, les autres au contraire en tarissant la sécrétion et rendant la stimulation des nerfs sécréteurs inefficace. Parmi les premiers, le plus anciennement connu est la pilocarpine, alcaloïde du Jaborandi, le type des seconds est l'atropine. Pour expliquer ces phénomènes il a été longtemps classique d'admettre que l'action des poisons portait sur les nerfs eux-mêmes : la pilocarpine excitait la corde du tympan et provoquait ainsi la sécrétion — au contraire l'atropine paralysait la corde du tympan. La mise en jeu ou l'inhibition de la sécrétion se faisaient par l'intermédiaire des nerfs.

(1) Ces Archives, vol. 57, p. 141.

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