LITERATURVERZEICHNIS

1. — E. B. VERNEY. *Verhandlungen der Deutsch. pharmakologischen Gesellschaft.* XV. Tagung. S. 24-37.
2. — W. RAUB. *Wiener Arch. f. innere Medizin. 17*, 472, 1929.
3. — F. R. STREGGERDA a. H. S. ESSEX. *Proc. soc. biol. a. med., 32*, 425.
4. — GIBBS. *Journ. of Pharmacol. 40*, 1930.
5. — THOMPSON. *Du Bois-Reymonds Arch. f. Physiol.* 1894. S. 117. Zit. nach LŒWI (6).
6. — LŒWI. *Arch. f. exp. Path. 48*, 429, 1902.
7. — WALTI. *Arch. f. exp. Path. 36*, 114, 1895.
8. — DOUGLAS COW. *Arch. f. exp. Path. 69*, 402, 1912.
9. — GINSBERG. *Arch. f. exp. Path. 69*, 381, 1912.
10. — R. I. PENCHARZ, J. HOPPER Jr., E. H. RYNEARSON. *Proc. Soc. Biol. a. Med. 34*, 14.
11. — W. MAHONEY and D. CHEEHAN. XV. Internal. Physiologen-kongress, Leningrad-Moskau, 1935.

FROM THE DEPARTMENT OF MEDICAL CHEMISTRY,
UNIVERSITY OF UPPSALA, SWEDEN

KINETICS OF DISTRIBUTION OF SUBSTANCES ADMINISTERED TO THE BODY

I. The Extravascular (*) Modes of Administration

BY

TORSTEN TEORELL

(Received for publication 21-6-1937.)

INTRODUCTION

In the administration of a drug or some other substance to the human or animal body so very frequently performed by the physician or the physiologist, most of the interest so far seems to have been focussed on more practical points such as testing the proper dosage or suitable ways of administration, or on the finer mechanism involved in the effects produced by the drug. Very little work seems to have been devoted to the *kinetics*, i.e. the time relations of the drug action.

It has been found that the effects, not only in regard to quantity but sometimes also in regard to quality, are dependent upon the drug concentration within a certain tissue or organ or its " milieu intérieur " (CLAUDE BERNARD), i. e. the circulating blood or lymph. The drug concentration in its turn is, as is wellknown, bound to be a function of time, because the processes of resorption, distribution, consumption, or elimination of the drug require time. It would therefore be expected that studies of the kinetics of these processes might be valuable in attempts to explain the relation between administration modus and physiological effect, which is emperically observed in many cases. Furthermore, if general principles on the kinetics of resorption, distribution, etc., could be laid down and expressed in mathematical formulas, which could be tested and confirmed experimentally, one could read off directly from such formulas *how*

(*) The intravascular (intraveneous) injection form will be treated in a following communication.

different factors influence the time relations between the dose given, etc., and the concentration of the substance in question in the blood or in a certain tissue. It might very well be possible, by aid of relations derived, to find out which is the best way to dose and to administer a drug, or even how to *change* the drug, in order to ascertain a definite time-concentration relation and thereby a desired therapeutical effect.

Notes on the Ways of Administration.—A drug or any other substance is most frequently given into the digestive channel "*per os*" and in rare cases "*per rectum.*" A great many medicaments are administered "parenterally" by various types of injections, for instance by *subcutaneous, intramuscular* or *peritoneal* injections. There is also the most direct way, the *intravascular* injection, usually in the intraveneous form. Direct injection into the blood vessels may be "prompt," when the whole dose is given at one time as a "massive dose," or a continuous or "drop" injection if the dose is administered in a continuous flow over a longer period (in German "Dauer-Injektion"). The *inhalation,* for instance of volatile anaestetics, may be regarded as a special form of a continuous administration.

Earlier Literature.—There are rather few investigations published on this subject of such importance from a physiological and medical point of view. E. WIDMARK (1) has paid particular interest to the kinetics of the distribution of several narcotics, especially of alcohol, and has published a number of fine researches, conducted both experimentally and theoretically. Several authors have carried out experiments using dye stuffs and have found regular time courses of the elimination from the blood, and have applied mathematical treatment [for instance, SMITH (3), HEMINGWAY and collaborators (4)]. In a series of papers DOMINGUEZ and his collaborators (5,6) have dealt with the kinetics of the elimination of creatinine, urea and xylose. In regard to the theoretical treatment DOMINGUEZ (5*a*) seems to have made an erroneous fundamental assumption which leads to false conclusions; this will be discussed in detail later (p. 218). Quite recently WIERZUCHOWSKI (7) has carried out experiments on glucose concentration in the blood after intraveneous injections continued over a longer period. To this incomplete list of authors dealing with this subject should be added LŒWE (8), who has taken some interesting view in his monograph on quantitative pharmacology. Some further papers will be mentioned later in connection with the presentation of the results.

The experimental and theoretical investigations so far, however, are in several respects very incomplete. Experiments with quantitative determinations have been confined to concentrations in the blood or urine. Very few papers give figures on the tissue concentration [WIDMARK (1*b*), GYLLENSVAERD (9)]. DOMINGUEZ, however, has attempted a balance account and has been able to follow more than 90 per cent of an injected substance (5*a*). The mathematical formulations have either been of a pure formal nature [for instance, HEMINGWAY and collaborators (4)] or have been restricted to very limited special cases. WIDMARK's formula, for instance, for the blood alcohol cumulation curve is valid only for the "post-resorptive" period. DOMINGUEZ has been interested only in the intraveneous form of administration.

Owing to these circumstances it seems justified to carry out a more thorough theoretical investigation. The object of this work will consist in the derivation of general mathematical relations from which it is possible, at least for practical purposes, to describe the kinetics of distribution of substances in the body. Time-concentration curves will be presented as illustrations to the relations derived.

It is hoped that the results presented will stimulate further experimental work on these matters.

THE GENERAL FACTORS GOVERNING THE TRANSPORT OF MATERIAL IN BIOLOGICAL SYSTEMS

It seems practical to regard the distribution of a drug as occurring in series of consecutive processes or steps, such as sketched in FIG. 1 (page 210). For instance, following a subcutaneous injection we may have the following sequence of transference : (1) From the subcutaneous depot to the blood; (2) From the blood to the tissues; (3) From the blood to the kidney (lungs, bile, etc.) for elimination; (4) In the tissues a form of "inactivation" may take place. This may consist in a chemical reaction, adsorption, etc., or some other process. In the steps (1), (2) and (3) transport of the drug molecules or ions across boundaries is involved. These boundaries are of a very complex nature, composed of cell formations of various types, built up by porous or liquid cell membranes and protoplasmic layers, etc. In reality the transportation across the boundaries will not be as simple as diffusion across a porous membrane, such as the collodion or parchment membrane used in model experiments.

In general, it may be stated that the permeation across cell or tissue boundaries, called "resorption," "adsorption" or "elemination" in the medical and biological literature, is dependent upon the *permeability* of the drug molecules or ions and the *driving forces* acting upon them. By the term permeability as used here we mean a factor inverseley related to the frictional resistance, or more strictly speaking we might call it the net effects of all frictional resistances encountered by the penetrating drug particles during the passage across a boundary. The driving forces pushing the particles across are mainly of two kinds in the body :

(1) The *(partial) osmotic pressure gradient*, which, just as a difference in gas pressure, causes the particles to move from a place with a higher pressure to one with a lower. In the following we will instead use the term *concentration gradient*, which may amount to approximately the same. This force acts equally on both molecules and ions.

(2) The second force is the *electrical potential gradient* that may be present in the cell or tissue elements. This force has of course only influence upon electrically charged particles i.e. the ions or the colloid particles and without effect on the undissociated molecules. The origin of the electric force may be traced to a diffusion potential, membrane effects, diphasic boundary potentials, etc. [cf. TEORELL (10)].

The osmotic or concentration gradient force strives to make all

concentrations (1) equal; the electrical potential gradient tends to make them unequal. Both forces are superimposed and act simultaneously. According to the direction of the electrical potential this force may work either in the same direction as the concentration gradient and thus create an increased pull on the particles, or, the forces may counteract each other and thereby decrease the pull [cf. NERNST (11), PLANCK (12) ARRHENIUS (13)]. It is due to this cooperation of two forces that we sometimes can observe a steady difference in the distribution of a particular substance across a membrane, fully permeable to the substances. It is very probable that many such distribution differences in the biological systems, now ascribed as lacking permeability, in reality are apparent equilibria (" Scheingleichgewichte," steady states) caused by such a play of forces. Another phenomenon that may have the same explanation is known as " retrograd diffusion " in cases where it is observed that particles can move " up hill " against the concentration gradient [BEHN (14), THOVERT (15), OSBORNE (16), WALPOLE (17)]. and thus create a substance accumulation or the reverse [STRAUB (18), TEORELL (10 *b* and *c*)].

In this treatment we have not considered the influence of preferential solubility or partition, nor of water streaming. It is probable, however, that in regard to the kinetics in the body, the effects played by solubility and even of water movements may be accounted for by the complex permeability coefficients to be used.

A quite general mathematical treatment of the kinetics of distribution valid also for electrolytes or colloid substances, although quite possible to perform, would be far too complex to be profitable. Among other things such calculations would need knowledge of the potential differences at the tissue boundaries concerned. At present very little such knowledge is available. Fortunately, however, a great number of pharmacological and other substances are non-electric in character or, if electrical effects are displayed, they are in many instances rather small. In such cases the whole matter will be greatly simplified in so far as only the osmotic forces, i.e. concentration gradients need to be considered in the mathematical discussions. It should be strongly emphazised that all the simplifications mentioned, although practically necessary, involve a certain degree of limitation in the applicability of the results presented. This should be particularly remembered when dealing with strong electrolytes. However, the

(1) Activity, or other more strict thermodynamic concepts as well as partition phenomena are neglected. The effects of " surface forces " are also disregarded in this discussion.

experimental evidence available at present, on the whole, seems to support the results of the simplified theory quite satisfactorily (cf. p. 217, 218).

FUNDAMENTAL ASSUMPTIONS

Because of the reasons just given we confine our investigations to cases where the electrical forces are weak or to cases concerned with the administration of non-electrolytes.

The *amount* of the drug, which permeates a certain tissue boundary, is assumed to depend on FICK's wellknown law for unidimensional, molecular diffusion [JACOBS (19)] :

$$\underset{-\,dN}{\textit{Amount}} = \underset{D}{\textit{diffusion coeff.}} \times \underset{dc/dx}{\textit{conc. gradient}} \times \underset{A}{\textit{surface}} \times \underset{dt}{\textit{time}} \qquad \text{(Eq. 1)}$$

Provided the thickness of the diffusion layer, i.e. the tissue boundary, is small enough, a constant (straight line) concentration gradient will be established within a very short time (cf. JACOBS, *l. c.*, p. 63), therefore dc/dx in Eq. 1 can be substituted by the concentration difference prevailing across the tissue boundary. It seems reasonable to assume that most tissue boundaries will fulfill this condition; the distance, for instance, between a blood capillary and even a very distant tissue element does not exceed, say, 0,1 millimeter. According to JACOBS (*l. c.*, p. 63) a constant rate of passage would be practically attained within a few seconds using that thickness.

The diffusion coefficient is related to the net value of the friction coefficients encountered (cf. p. 207) and it will be incorporated together with the effective permeation surface and the boundary thickness in a " permeability coefficient " as k_n' in the following.

FICK's law, Eq. 1, may now be rewritten as

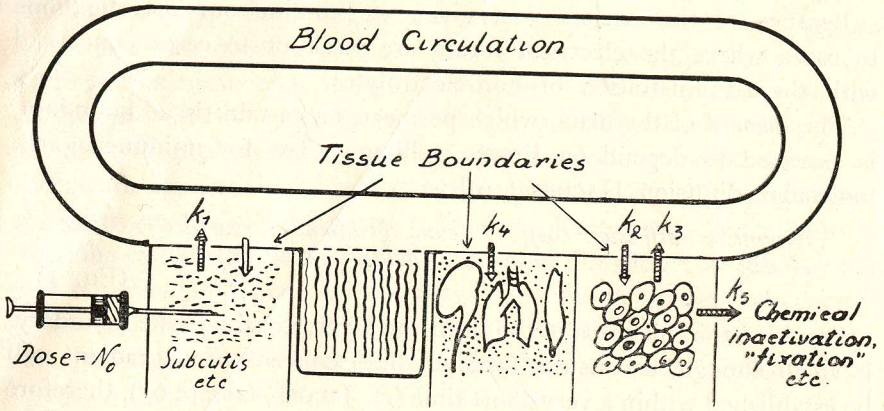
$$\underset{-\,\frac{dN}{dt}}{\textit{Amount Across Boundary in the Time Unit}} = \underset{k_n'}{\textit{Permeability Coefficient}} \times \textit{Concentration Difference} \left(\frac{N_i}{V_i} - \frac{N_o}{V_o}\right) \qquad \text{(Eq. 2)}$$

where N_i, V_i and N_o, V_o are the amount of the drug and the fluid volume respectively inside and outside the boundary, and " amount " is the number of gram molecules or grams or any unit. *Concentration* figures are obtained, if desired, by division of " *amount* " with the

appropriate volume. Eq. 2 is the fundamental equation for a reversible process, which will be applied in the following.

We picture the drug distribution as taking place according to the scheme pictured in FIG. 1, where the significance of the symbols used are indicated.

Besides the " permeability coefficients," which are a measure of



Local	Drug depot	Blood + equivalent Blood vol	Kidney etc elimination	Tissues	Tissue inactivation
Symbol	D	B	K	T	I
Amount	x	y	u	z	w
Volume	V_1	V_2	—	V_3	—
Concentration	x/V_1	y/V_2	—	z/V_3	—
Perm. coeff	k_1'	—	k_4' .	k_2'	—
Velocity constant out	$k_1 = k_1'/V_1$	—	$k_4 = k_4'/V_2$	$k_3 = k_2'/V_3$	k_5
Velocity constant in	neglected	—	not existing	$k_2 = k_2'/V_2$	—
Name of process	Resorption	—	Elimination	Tissue take up -"- output	Inactivation

FIG. 1

Scheme of the Concept of Drug Distribution used in this paper.
Instead the *injection* pictured in the figure, the administration of the drug depot can be made *per os, per rectum, by inhalation,* etc.

the permeability (cf. p. 209) of the tissue boundaries, we introduce the " velocity constants," which are the former divided by the appropriate volume. The latter constant is a measure of the *intensity* of passage or inactivation.

EQUATIONS OF THE VARIOUS DISTRIBUTION PROCESSES

We have the following steps :

a) *Depot-Blood Passage (" Resorption ").*—The administered drug depot can be *enteral* (per os), *subcutaneous*, *intramuscular*, etc. (in general any form of depot). The fundamental Eq. 2, describing the rate of passage, applied here, is written :

Rate of Resorption = Proportional to Conc. Difference Depot-Blood

$$-\left(\frac{dN}{dt}\right)_{D\text{-}B} = k_1'\left(\frac{x}{V_1} - \frac{y}{V_2}\right) \qquad \text{(Eq. 3}a\text{)}$$

In most cases the depot volume V_1 is very small compared with V_2, the blood + equivalent blood volume (1). In man V_2 is more than 5 liters, but V_1 seldom exceeds 50 cc. Furthermore V_1 in general decreases because of a simultaneous fluid resorption. Accordingly the velocity constant for the passage out of the depot, k_1'/V_1 is at least 100 times greater than k_1'/V_2. It becomes evident from simple discussions that the second term in Eq. 3*a* therefore can be neglected, and we may write instead *the resorption rate proportional to the depot concentration* :

$$-\left(\frac{dN}{dt}\right)_{D\text{-}B} = \frac{k_1'}{V_1} \cdot x \quad \text{or} \quad k_1 \cdot x \qquad \text{(Eq. 3}b\text{)}$$

The possibility of substituting Eq. 3*a* by Eq. 3*b* considerably simplifies the treatment. The use of Eq. 3*a* would lead to a third degree equation on the further solution of the simultaneous equation system and would introduce trigonometrical roots which would make the results very cumbersome.

b) *Blood-Kidney Passage (" Elimination ").*—This is an irreversible process going one direction only, and whatever the actual mechanism may be, it seems still justified (2) to apply FICK's law, Eq. 2, neglecting the second concentration term, thus putting *the elimination rate proportional to the concentration in blood :*

$$\left(\frac{dN}{dt}\right)_{B\text{-}K} = k_4' \cdot \frac{y}{V_2} \quad \text{or} \quad k_4 \cdot y \qquad \text{(Eq. 4)}$$

(1) In regard to the wide interpretation of the volume V_2 used here, see p. 216.
(2) For discussions see DOMINGUEZ's works.

Besides the kidney, the organ of elimination may be the lungs, the intestines, the liver, the bile system, etc.

c) *Blood-Tissue Passage (" Tissue Take up," " Tissue output ").* —Here we meet a bothway process. The fundamental Eq. 2 applied here states that *the rate of passage is proportional to the prevailing concentration difference* between the blood and the tissue :

$$\left(\frac{dN}{dt}\right)_{B\text{-}T} = k_2'\left(\frac{y}{V_2} - \frac{z}{V_3}\right) \text{ or } (k_2 \,.\, y - k_3 \,.\, z) \qquad \text{(Eq. 5)}$$

During the early stages the blood concentration of the drug is higher than the tissue concentration and there is a " take up." Later, however, the blood concentration may pass under that of the tissue as an effect of the kidney elimination and there may arise a reversal of the direction of substance passage. At the moment of the change of direction, the blood concentration and the tissue concentration are obviously equal (1) (cf. FIG. 3), (this, however, is true only when the substance inactivation in the tissue is not taken into consideration).

d) *The Tissue Inactivation*—regarded as irreversible, may occur owing to chemical destruction, for instance by oxidation, coupling to other substances, etc., or is caused by some kind of irreversible storage [SMITH (3) has shown that some dyes may be taken up by certain cell elements]. It seems very probable that such processes follow the course of a " monomolecular reaction," i.e. *the rate of inactivation at any instant is proportional to the substance concentration at that time*, or

$$\left(\frac{dN}{dt}\right)_{I} = k_5' \,.\, \frac{z}{V_3} \quad \text{or} \quad k_5 \,.\, z \qquad \text{(Eq. 6)}$$

SOLUTIONS OF THE DIFFERENTIAL EQUATIONS

The aim of this investigation was to present explicit expressions for the amount of drug in the depot, blood and tissue (named x, y and z respectively) and the amount eliminated from the body and inactivated in the tissues (named u and w), all as functions of time, t, and permeability, the latter being measured in terms of the permeability or velocity constants (k_1 to k_5). These expressions will now be derived by means of Eqs. 3*b*, 4, 5 and 6.

(1) Here DOMINGUEZ et al. are in error as they state that maximum tissue concentration occurs earlier while the blood concentration is greater than the tissue concentration, cf. p. 218.

a) The substance amount in the blood tends to be *increased* because of " resorption " from the depot (Eq. 3*b*) and to be *decreased* due to kidney elimination, etc. (Eq. 4) and due to substance passage to the tissue (Eq. 5). Accordingly the rate of change of the amount in the blood dy/dt, can be expressed by the equation

$$\frac{dy}{dt} = \underbrace{k_1 \,.\, x}_{\text{Eq. 3}b} - \underbrace{k_4 \,.\, y}_{\text{Eq. 4}} - \underbrace{(k_2 y - k_3 z)}_{\text{Eq. 5}} \qquad \text{(Eq. 7)}$$

If it happens that $\frac{y}{V_2} < \frac{z}{V_3}$ the parenthesis term changes the sign indicating passage *to* the blood instead of passage *from* it.

The term $k_1 \,.\, x$ from Eq. 3*b*, expressing that the resorption rate at any instant is proportional to the depot concentration, can at once be integrated to give *the time dependance of the depot amount*

$$x = N_0 \,.\, e^{-k_1 \cdot t} \qquad \text{(Eq. 8)}$$

where N_0 denotes the total amount of the substance which was initially administrated, that is the " dose." The equation now contains only two unknown variables y and z.

b) The rate of change of the *tissue* drug amount, dz/dt, depends on the passage between blood and tissue (Eq. 5) and the rate of tissue inactivation (Eq. 6) in the following manner :

$$\frac{dz}{dt} = \underbrace{(k_2 y - k_3 z)}_{\text{Eq. 5}} - \underbrace{k_5 \,.\, z}_{\text{Eq. 6}} \qquad \text{(Eq. 9)}$$

c) In order to facilitate the calculations we introduce symbolic differentiation, making use of the " operator " D (which here stands for d/dt) (1).

We can now rewrite Eqs. 7 and 9 as the following system of linear, simultaneous differential equations (x in Eq. 7 is substituted by help of Eq. 8)

$$\begin{cases} [D + (k_2 + k_4)]y - k_3 z = k_1 \,.\, N_o \,.\, e^{-k_1 t} & \text{(Eq. 7}a\text{)} \\ -k_2 y + [D + (k_3 + k_5)]z = 0 & \text{(Eq. 9}a\text{)} \end{cases}$$

This system contains only two unknowns and can be solved the ordinary way by substitution. It is more convenient, however, to use " determinants " for the solution of simultaneous equations (1).

(1) Concerning the use of this it may be referred to text books of higher mathematics, for instance MELLOR (20), p. 396 and 580.

Solution of the Drug Amount in the Blood (y).—In regard to y we may write Eqs. 7*a* and 9*a* in determinant form as

$$\begin{vmatrix} [D + (k_2 + k_4)] & -k_3 \\ -k_2 & [D + (k_3 + k_5)] \end{vmatrix} y = \begin{vmatrix} k_1 . N_o . e^{-k_1 t} & -k_3 \\ o & [D + (k_3 + k_5)] \end{vmatrix}$$

which leads to following expression, where p and q have the significance given in Eqs. 12 and 13,

$$D^2 + pD + qy = k_1(k_3 + k_5 - k_1) . N_o . e^{-k_1 t} \qquad \text{(Eq. 10)}$$

This second order differential equation is solved by ordinary methods by addition of a "complementary function" and the appropriate "particular integral" (1). The complete solution is written :

$$y = C_1 . e^{m_1 t} + C_2 . e^{m_2 t} + S . e^{-k_1 t} \qquad \text{(Eq. 11)}$$

where the new symbols are abbrevations as follows :

$$p = (k_2 + k_3 + k_4 + k_5) \qquad \text{(Eq. 12)}$$

$$q = (k_2 k_5 + k_3 k_4 + k_4 k_5) \qquad \text{(Eq. 13)}$$

$$m_1 = -0.5p + \sqrt{0.25p^2 - q} \qquad \text{(Eq. 14)}$$

$$m_2 = -0.5p - \sqrt{0.25p^2 - q} \qquad \text{(Eq. 15)}$$

$$C_1 = \frac{k_1 N_o + S(k_1 + m_2)}{m_1 - m_2} \qquad \text{(Eq. 16)}$$

$$C_2 = -\frac{k_1 N_o + S(k_1 + m_1)}{m_1 - m_2} \qquad \text{(Eq. 17)}$$

$$S = \frac{(k_3 + k_5 - k_1)k_1}{k_1(k_1 - p) + q} . N_o \qquad \text{(Eq. 18)}$$

The constants C_1 and C_2 in the Eq. 11 are integration constants, their values are found to be expressed as Eqs. 16 and 17 by use of the initial condition : $t = 0$, $y = 0$. The third term in Eq. 11 is the particular integral derived from Eq. 10.

Solution of the Drug Amount in the Tissues (z).—Is performed from the same system, Eqs. 7*a*, 9*a*, as was used above and in a similar manner.

(1) Cf. textbooks (MELLOR, p. 399 and 418).

The equation obtained for z is of the same general type as for y, or

$$z = R_1 . e^{m_1 t} + R_2 . e^{m_2 t} + H . e^{-k_1 t} \qquad \text{(Eq. 19)}$$

The new constants are abbrevations as follows :

$$R_1 = \frac{(k_1 + m_2)}{m_1 - m_2} . H \qquad \text{(Eq. 20)}$$

$$R_2 = -\frac{(k_1 + m_1)}{m_1 - m_2} . H \qquad \text{(Eq. 21)}$$

$$H = \frac{k_1 k_2}{k_1(k_1 - p) + q} . N_o \qquad \text{(Eq. 22)}$$

Solution of the Drug Amount Eliminated through the Kidneys, etc. (u). According to Eq. 4 we have

$$\textit{Elimination per Time Unit} = k_4 . y \qquad \text{(Eq. 4)}$$

By direct integration we find that

$$u = \textit{Total Amount Eliminated} = k_4 \int_o^t (y) dt + \text{const.}$$

If y is substituted from Eq. 11 the value of the integral is obtained as

$$u = k_4 \left[\frac{S}{k_1}(1 - e^{-k_1 t}) - \frac{C_1}{m_1}(1 - e^{m_1 t}) - \frac{C_2}{m_2}(1 - e^{m_2 t}) \right] \qquad \text{(Eq. 23)}$$

where the symbols have the same significance as before (Eqs. 12 to 18).

Solution of the Drug Amount Inactivated in the Tissues (w).—Eq. 6 stated that

$$\textit{Inactivation per Time Unit} = k_5 . z \qquad \text{(Eq. 6)}$$

Accordingly we find in analogy with the derivation of u that

$$w = \textit{Total Amount Inactivated} = k_5 \int_o^t (z) dt + \text{const.}$$

and by aid of Eq. 19

$$w = k_5 \left[\frac{H}{k_1}(1 - e^{-k_1 t}) - \frac{R_1}{m_1}(1 - e^{m_1 t}) - \frac{R_2}{m_2}(1 - e^{m_2 t}) \right] \qquad \text{(Eq. 24)}$$

The significance of the symbols is identical as in Eqs. 12-15, 20-22.

Results and conclusions

The preceding study on the kinetics of the distribution of an administrated drug or other substance has made it possible to express the actual amounts involved as functions of time, " permeability coefficients " (and volumes). In order to obtain *concentrations*, if they are desired, the " amount " results must be divided by the corresponding volumes (of depot, tissue, etc.). The resulting formulas are summarized :

depot amount	Equation 8, p. 213
blood amount	,, 11, p. 214
tissue amount	,, 19, p. 215
eliminated amount	,, 23, p. 215
inactivated amount	,, 24, p. 215.

By means of these formulas and the auxillary equations 12-18, 20-22 it is possible to perform numerical calculations using any values assigned to permeability coefficients, volumes and time.

The results of such calculations are graphically reproduced in Fig. 2-7. In all cases only such assumptions have been made in regard to the relative magnitude of the constants that actually may occur in the animal body. However, all measures are necessarily of a relative nature, " amount " figures being given in per cent of dose, and " time units " used instead of hours and so on.

Some comments will be made below, in regard to the results shown in the diagrams. It should be strongly emphazised, that when speaking of " blood," it has always been understood that the term includes the blood, the lymph and other intercellular liquid and also those tissues, which practically instantaneously come into equilibrium with the blood plasma in regard to the particular substance exchange (" equivalent blood volume "). Dominguez uses the collective term " equivalent plasma volume." He offers evidence that this can be 1/4 of the body weight. " Tissue " is here used as an average concept, because it is likely that the various anatomical tissues may behave very differently in their ability of taking up or inactivating a certain substance. Widmark (1*a*) introduced a similar concept in his researches, called " reduced bodily volume," which he found in man (by use of acetone) to be around 3/4 of the body weight, blood volume included. Dominguez (5*a*), using creatinine, determined the " tissue volume " and the " equivalent plasma volume " to be about 1/2 and 1/4 respectively of the

body weight (on dogs). The ratio V_3/V_2 i.e. *tissue volume* : *blood volume*, in the sense used here, can according to these authors be estimated to have the order 3 : 1 or 2 : 1. In our calculations the ratios are 2 : 1 or 1 : 1.

1. *A Typical Case.*—The time course represented in Fig. 2 may be regarded as typical for the distribution of a drug in the body following, say, a subcutaneous injection (1). First, by looking at the *blood* curve it is observed that the drug accumulates very rapidly during a comparatively short initial period following the injection, the amount, however, soon reaches a maximum value and later decreases rather slowly. It is easy to show that this decrease is approximately exponential, because when t, the time, is sufficiently large, the second and third terms in Eq. 11 vanish and only a single exponential remains. Incidentally, this is exactly what Widmark has observed experimentally, the " post-resorptive period " following acetone administration showed a concentration decrease, which fitted very nicely into a simple exponential formula [cf. also Gyllensvaerd (9)]. Statements in regard to the location of the time and the height of the maximum value will be deferred till later (p. 221).

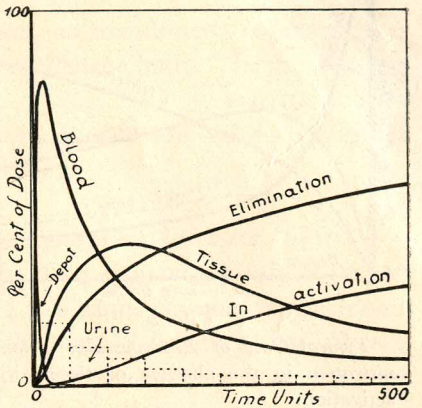


Fig. 2

Typical Case of Extravascular (such as *per os* or *subcutaneous*) *Administration* in the presence of both elimination and tissue inactivation.*

Dotted bars indicate output in urine samples taken at equidistant intervals. ($k_1 = 0.2$; $k_2 = 0.01$; $k_3 = 0.005$ i.e. the ratio " blood " volume/" tissue " volume is 1 : 2; $k_4 = 0.005$; $k_5 = 0.002$.)

The *tissue* curve may perhaps be the most interesting one from a medical and physiological point of view, because it is in and from the tissues that the pharmacological effects are displayed. We see in Fig. 2 that the z curve never reaches as high values as the blood curve, particularly if we take into consideration that the z values must be reduced to 1/2 size, when the actual concentration figures instead

(1) It should be remembered that intramuscular, intraperitoneal or enteral (also *per os*) administrations behave analogously, cf. the assumptions on p. 210.

* Inactivation in the *blood* is formally equivalent to the expressions for the elimination (through kidneys, etc.).

of the absolute " amount " values are compared. Further it is to be noted that the amount (and concentration) maximum in the tissues is attained at a much later time than in the blood. If no tissue inactivation is going on, the curves in FIG. 3 are valid. As is obvious, the z values there are larger, and the whole z-curve has a more prolonged course than in FIG. 2. It should be observed that the relative tissue *concentration* curve, which also is drawn in FIG. 3, has its maximum when it crosses over the blood curve as we previously pointed out on p. 212.

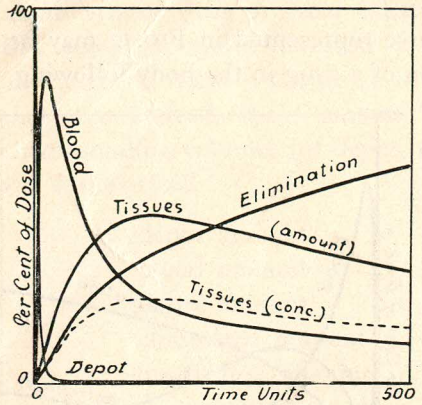


FIG. 3

Typical Case of Extravascular Administration in the absence of tissue inactivation.

($k_1 = 0.2$; $k_2 = 0.01$; $k_3 = 0.005$; i.e. " blood " volume/" tissue " volume is 1 : 2; $k_4 = 0.005$; $k_5 = 0$).

The only pieces of experimental evidence in regard to the last statement that seem to be available at present, are a number of curves first presented by ABRAMSON and LINDE (21) and later work by FLEMING and STOTZ (22) which on the whole fairly well support the relations between blood and tissue concentration predicted here. These authors determined simultaneously the concentration figures in the blood and the cerebrospinal liquid following alcohol consumption. Other evidence is presented in WIDMARK's monograph (1b).

DOMINGUEZ (5*a*) has derived an expression for the tissue concentration which from a formal point has the correct form (*l. c.*, Eq. 15) and which leads him to the conclusion that " the *concentration* in the tissues is consequently greatest some time *before* the equilibrium between the plasma and the tissues may be said to have been established " (*l. c.*, p. 243, cf. also his FIG. 1). This statement is true only when tissue inactivation is present (cf. our FIG. 2). DOMINGUEZ, however, has not considered any such inactivation and accordingly his conclusion is false (1).

The *elimination* and *inactivation* curves in FIG. 2 are S-shaped, and the points of inflexion coincide in time with the " peak " value of the blood and tissue amount curve respectively, i.e. the rate of elimination and inactivation is at a maximum here. The tangents

(1) The error is made in DOMINGUEZ's fundamental proposition (*l. c.*, p. 242) that " the rate of diminution of the concentration difference is proportional to the concentration difference itself." This assumption is not correct when more than one diffusion process is involved. In DOMINGUEZ's own case, however, there is a " side by side " process to the blood-tissue diffusion, namely the elimination through the kidneys. The fact that DOMINGUEZ has dealt only with the intraveneous injection does of course not change this criticism. The intraveneous injection will be treated in a subsequent paper.

to the curves at the time zero and infinity are parallel with the time axis, i.e. the rates are zero. If we imagine that frequent urine collections are made with the same time interval, we should obtain a curve running nearly parallel to the blood curve when plotting the amount found in each sample against time. In FIG. 2 this is illustrated by the dotted bars. DOMINGUEZ (5*a*) has obtained a very satisfactory confirmation of this prediction in experiments on dogs by giving creatinine intraveneously.

The conditions shown in FIG. 2 are, as mentioned, regarded as a prototype for a substance distribution within the body. In the FIG. 3-7 some special cases are demonstrated.

In FIG. 3 the same conditions as in FIG. 2 are valid, but tissue inactivation is regarded as being absent.

2. *The Influence of Different Drug Resorption Intensity.*—FIG. 4 is thought to illustrate a case where the drug penetrates only to a part of the body tissues (assumed to have the same volume as the blood) and demonstrates at the same time *the marked influence that different depot resorption conditions* (k_1 varied) *have, particularly upon the blood and tissue time curves.* The tissue inactivation is not considered with exception of the case when $k_1 = 0{,}01$ where, for comparison, the dotted curve is drawn to show the influence of a moderate inactivation ($k_1 = 0{,}01$, $k_5 = 0{,}005$). Here the theoretical results have a particular pharmacological interest in view of several practical efforts made during recent years to modify the physiological effect of certain substances by altering the resorption properties. In order to obtain a more prolonged effect and a less violent initial effect (" shock ") insulin, among other things, has been subjected to various chemical treatments such as coupling to protamin [HAGEDORN and collab. (23)] or to zinc compounds [SCOTT and FISHER (24) and others]. *The empirical idea of these authors that a decrease in the resorptivity can give a more suitable distribution in the tissues agrees with the presented theoretical results.*

As a general rule we can state *that the slower the depot resorption the lower the concentration in the tissue (and blood) becomes and the later the concentration maximum appears* (FIG. 4*b* and *c*). This is true whether tissue inactivation is present or not. The exact mathematical relations are not easily expressed for the general case. For somewhat simplified conditions, however, the relationship is obtained very clearly cut in the following way, by assuming that the drug is taken up only by a tissue portion whose volume is small compared with the blood

volume (" blood " is taken in the wider sense, cf. p. 216). Then we can almost neglect the tissue distribution, i.e. in the formula for the blood curve (Eq. 11) we insert k_2, k_3 and k_5 as equal to zero. Then we obtain Eq. 11 in the special form :

$$y \left.\begin{matrix} k_2 \\ k_3 \\ k_5 \end{matrix}\right\} = 0 = \frac{k_1}{k_4 - k_1} N_o(e^{-k_1 t} - e^{-k_4 t}) \qquad \text{(Eq. 25)}$$

The graphical representation of y will have a similar course as before. Eq. 25 is of a type wellknown in chemistry as valid for " two consecutive

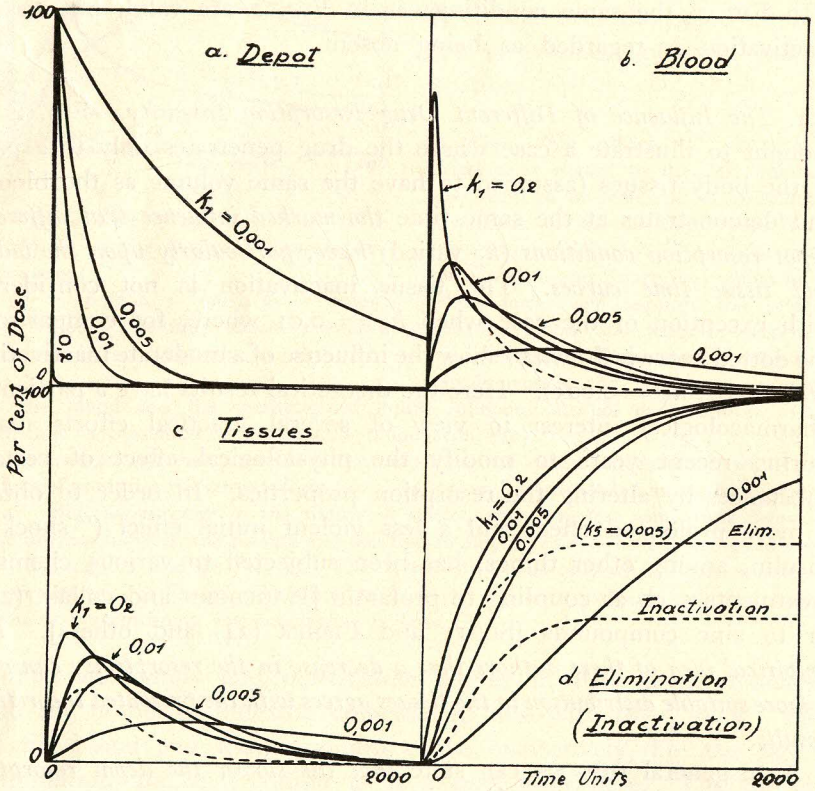


FIG. 4

Extravascular Administration at different degrees of drug resorptivity.

The figure shows the marked influence that a change in the resorptivity (from the depot to the blood) has upon the cumulation curves in the blood or the tissues.

Tissue inactivation (dotted line) is considered only for the case $k_1 = 0.01$. ($k_1 = 0.2$; 0.01, 0.005 or 0.001; $k_2 = 0.01$; $k_3 = 0.01$ i.e. "blood " volume/" tissue " volume is 1 : 1; $k_4 = 0.005$; k_5 = zero or 0.005).

monomolecular reactions ". (1). Corresponding to the two reactions we have here the depot resorption and the kidney elimination. The maximum conditions of Eq. 25 are derived in the usual way, by differentiating with respect to time, t, equating the derivative to zero and in an appropriate way solving for the t-maximum and the y-maximum. The results are :

$$t_{max.} = \frac{2.3}{k_1 - k_4} \log \frac{k_1}{k_4} \qquad \text{(Eq. 26)}$$

$$y_{max.} = N_o \left[\frac{k_1}{k_4}\right]^{\frac{k_4}{k_4 - k_1}} \qquad \text{(Eq. 27)}$$

In words the equations express that

a) *The time of the maximum is independent of the dose administered* (because N_o does not appear in formula 26). *A diminution of the depot resorption rate* (k_1 diminished) *causes the maximum time to appear later* (cf. p. 219 and FIG. 4*b*). In regard to the value of the y-maximum expressed in Eq. 27 we can state that

b) *The maximum drug amount circulating in the blood is directly proportional to the dose given* (N_o) *and approximately directly proportional to the depot resorption intensity* (k_1) *and inversely proportional to the elimination intensity* (k_4). The last approximation is closer to the truth, the smaller k_1 is compared with k_4, the exponent thereby approaches 1. This conclusion can roughly be extended to the *tissue* conditions, the more rapidly the tissue takes up the drug.

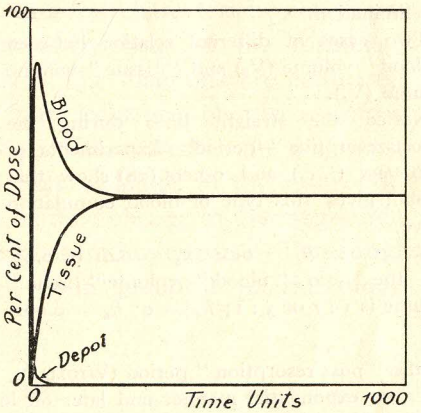


FIG. 5

A Case of Extravascular Administration in the absence of any elimination or tissue inactivation.

(Real blood volume + equivalent blood) and " tissue " volume regarded as equal ($V_2 = V_3$).

($k_1 = 0.2$; $k_2 = 0.01$; $k_3 = 0.01$; $k_4 = 0$ and $k_5 = 0$).

3. *Some Further Special Cases* of substance distribution in the body are represented in FIG. 5, 6 and 7. In the case pictured in FIG. 5 the conditions are the same as for one of the curves in FIG. 4 ($V_3/V_2 = 1$; $k_1 = 0{,}2$; $k_2 = k_3 = 0{,}01$)

(1) For instance transformation of radioactive substances, RUTHERFORD (25). OSTERHOUT (26) has used an analogous equation for consecutive, simultaneous diffusion processes. For a direct derivation cf. also HOAGLAND (27).

but it is assumed that the kidney elimination and tissue inactivation both are zero.

FIG. 6 illustrates the same case as FIG. 5, but while there still is no elimination, a slight inactivation is now present. Two different tissue volumes are considered.

FIG. 7 shows the conditions of FIG. 5 with an elimination present instead of inactivation.

In both the later cases we notice that after having reached the maximum, i.e. during the " post resorption " period (WIDMARK, *l. c.*), the blood-amount curve first decreases in an exponential manner and later on in a more or less straight line. The straight line falling off curves on blood alcohol described by WIDMARK and others (28) seem to belong to the class of curves pictured here.

The *y*-curves in FIG. 6 corresponds very closely to the curves on the disappearance of the dye " water blue " from the blood plasma published by HEMINGWAY and collaborators. They state that the kidney elimination of the dye is negligible and believe that the dye is taken up in the tissues by some special tissue elements (the reticulo-endothelial system). They have proposed a purely empirical formula for the time course of the disappearance which fits very closely with the experimental facts. The rational formula one should apply, however, should be Eq. 11 taking $k_4 = 0$ and also putting $k_1 = \infty$ because the intraveneous injection form was used by these authors. As we will show in the next paper in this series, the intraveneous application can be regarded as a limiting case of, say, the subcutaneous case, if we in the formulae put the resorption intensity, k_1, equal to infinity.

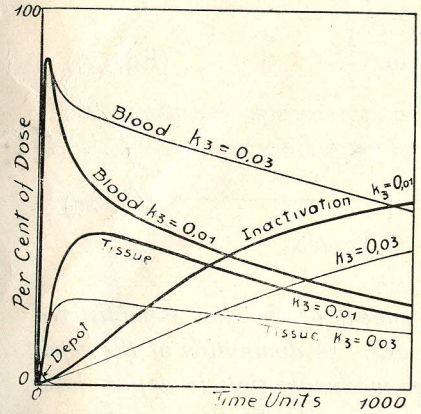


FIG. 6

Extravascular Administration in the absence of elimination.

Two cases of different relation between " blood " volume (V_2) and " tissue " volume volume (V_3).

Notice the straight lines during the " post-resorptive " period. Experiments of WIDMARK (*l. c.*) and others (28) show that alcohol gives this type of blood cumulation curve.

($k_1 = 0.2$; $k_2 = 0.01$; $k_3 = 0.01$ or 0.03, i.e. the ratio " blood " volume/" tissue " volume is 1 : 1 or 3 : 1; $k_4 = 0$; $k_5 = 0.002$.

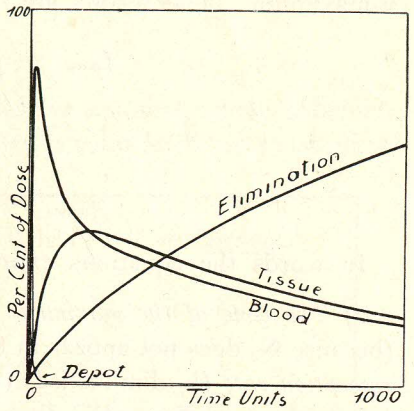


FIG. 7

Extravascular Administration in the absence of tissue inactivation.

Notice the almost straight lines during the later periods.

($k_1 = 0.2$; $k_2 = 0.01$; $k_3 = 0.01$ i.e. the ratio " blood " volume/" tissue " volume is 1 : 1; $k_4 = 0.002$; $k_5 = 0$.)

SUMMARY

The aim of this paper is to derive theoretical time-concentration relations which may be applied to the distribution of a drug or other substance which is administered to the body.

Some general principles which may be involved in the transport of material in living tissues are discussed. It is pointed out that in regard to kinetics the reasoning has to be reduced to two factors, the " permeability " and the " driving forces." The former may be rather complex in regard to the physical nature, the latter can be divided into osmotical and electrical parts. Because of lack of knowledge of the role played by electrical factors in the body the given treatment is restricted to the substance distribution caused by the osmotic force, i.e. the pure diffusion.

On the assumption that the distribution can be considered as a series of *simple diffusion* steps taking place *simultaneously* and in *succession*, formulae have been derived, which describe the amount or concentration of a drug in the depot, the blood, the tissues, the amount eliminated and inactivated, as a function of time and a few characteristic constants.

Numerical calculations are performed by help of the formulas. The results are represented graphically. The diagrams are compared with existing experimental results. The influence of the variation of various factors are discussed and in part illustrated in the diagrams. In particular, it has been emphazised that a change in the resorption properties of a drug may bring about a marked change in the magnitude and duration of the blood and tissue concentration curves. These and other conclusions may have bearings upon practical pharmacology and therapeutics.

BIBLIOGRAPHY

1. — *a*) WIDMARK, E. M. P., *Acta Med. Scand.* 1919, *52*, 87.
b) IDEM, Die theoretischen Grundlagen und die praktische Verwendbarkeit der gerichtlich-medizinischen Alkoholbestimmung. Berlin, 1932.
2. — WIDMARK, E. M. P. and TANDBERG, J., *Biochem. Z.* 1924, *147*, 358.
3. — SMITH, H. P. *Johns Hopkins Hospital Bull.* 1925, *36*, 325.
IDEM, *J. Exp. Med.* 1930, *51*, 369, 379, 395.
4. — HEMINGWAY, A. and collaborators, *Am. J. Physiol.* 1935, *112*, 56.

5. — Dominguez, R. and collaborators,
a) *Am. J. Physiol.* 1935, *114*, 240.
b) *J. Biol. Chem.* 1934, *104*, 449.
c) *J. Clin. Inv.* 1934, *13*, 753.
6. — Dominguez, R.,
a) *Proc. Soc. Exp. Biol. and Med.* 1934, *31*, 1146.
b) *Am. J. Physiol.*, 1935, *112*, 529.
7. — Wierzuchowski, K., *J. Physiol.* 1936, *87*, 311.
8. — Lœwe, S., *Ergeb. der Physiol.* 1928, *27*, 48.
9. — Gyllensvaerd, N., *Acta Med. Scand.* LXX, Suppl. XXII, 1935.
10. — Teorell, T.,
a) *Proc. Soc. Exp. Biol. and Med.* 1935, *33*, 382.
b) *Proc. Nat. Ac. Sci.* (U.S.A.), 1935, *21*, 152.
c) *J. Gen. Physiol.*, 1937, in press.
11. — Nernst, W., *Z. physik. Chem.*, 1888, *2*, 617; 1889, *4*, 154.
12. — Planck, M.,
a) *Sitzb. preuss. Akad. Wiss. Physik. Math. Kl.*, 1930, 367.
b) *Sitzb. preuss. Akad. Wiss. Physik. Math. Kl.*, 1931, 113.
13. — Arrhenius, S., *Z. physik. Chem.* 1893, *10*, 51.
14. — Behn, U., *Wiedemanns Ann. N. F.* 1897, *62*, 54.
15. — Thovert, J., *C. r. Acad. Sci.*, Paris, 1902, *134*, 826.
16. — Osborne, W. A. and Jackson, L. C., *Biochem. J.* 1914, *8*, 246.
17. — Walpole, G. S., *Biochem. J.* 1915, *9*, 132.
18. — Straub, J., *Kolloid-Z.* 1933, *62*, 13.
19. — Jacobs, M. H., *Erg. d. Biol.* 1935, *12*, 1.
20. — Mellor, J. W., Higher Mathematics for Students of Chemistry and Physics, London, New York, Toronto, 1931.
21. — Abramson, L. and Linde, P., *Arch. internat. de Pharm. et de Thérap.* 1930, *39*, 325.
22. — Fleming, R., and Stotz, E., *Arch. Neurol.* 1935, *33*, 492.
23. — Hagedorn, H. C., Norman Jensen, B., Larrup, N. B. and Wodstrup Nielsen, J., *J. Am. Med. Ass.* 1936, *106*, 107.
24. — Scott, D. A., and Fisher, A. M., *J. Pharm. and Exp. Ther.* 1936, *58*, 78.
25. — Rutherford, E., Radioactive substances and their relations, Cambridge, 1913.
26. — Osterhout, W. J. V., *J. Gen. Physiol.* 1933, *16*, 529.
27. — Hoagland H., Pacemakers in Relation to Aspects of Behavior, New York, 1935.

28. — Bernard, C. G., and Goldberg, L., *Acta Med. Scand.* 1935, *86*, 152.
— Neymark, Marit and Widmark, E. M. P., *Skand. Arch. Physiol.*, 1936, *73*, 283.
— Le Breton, E., Signification physiologique de l'oxydation de l'alcohol éthylique dans l'organisme. Lons-le-Saunier, 1936.

ARCHIVES INTERNATIONALES

DE

Pharmacodynamie et de Thérapie

FONDÉES PAR

E. GLEY, Paris et J. F. HEYMANS, Gand

PUBLIÉES PAR

C. HEYMANS, Gand et M. TIFFENEAU, Paris

AVEC LA COLLABORATION DE

Publiées avec le concours de la Fondation Universitaire de Belgique.

VOLUME LVII

GAND
RÉDACTION DES ARCHIVES
3, QUAI BAERTSOEN

PARIS
G. DOIN & Cie, ÉDITEUR
8, PLACE DE L'ODÉON

1937