termined immediately and continuously after the injection. It was observed that the average pressure of 88 mm of Hg before injection increased to a maximal average of 170 mm of Hg approximately two minutes after injection. Similar to the pressor response of the dog to renin, the pressures of the injected rats gradually fell after maintaining a plateau for approximately five minutes after injection. The pressures usually reached the control levels about 20 minutes after injection. Again similar to the dog, the rat was observed to develop tachyphylaxis rather quickly to injections of renin. Thus successive injections of the same amount of renin effected progressively smaller and more evanescent pressor effects and the third or fourth successive injection usually caused little or no rise in pressure.

Summary. The ability of the microphonic manometer to measure rapidly and simply not only the pressure of the intact rat but also of the rat made hypertensive by the injection of the vasoconstrictor substances, epinephrine and renin, indicates that it might be of considerable usefulness in studies necessitating frequent or successive blood pressure determinations in the rat.

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Kinetics of Distribution of Inulin Between Two Body Water Compartments.

MARIO GAUDINO.* (Introduced by Homer W. Smith.)
From the Department of Physiology, New York University College of Medicine, New York City.

The kinetics of distribution of inulin between the intravascular and the interstitial compartments after its introduction into the circulatory system is of interest in relation to the use of this substance as a measure of the extracellular volume.[1,2]

The present paper concerns the distribution of any substance with the properties of inulin between two fluid systems representing schematically the intravascular and interstitial compartments of the body.

Let V_1 be the volume† of the intravascular compartment (I) and V_2 the volume of the interstitial compartment (E), both of which will be assumed to remain constant during the experimental procedure. It is further supposed that the rate of mixing of the substance in each of these compartments is rapid compared to simple diffusion. If the concentration of the substance in I is represented by $c_1(t)$, the concentration in E by $c_2(t)$, the concentration in the urine (assumed to be the only route of elimination) by $c_3(t)$, and if the flow (q_1) of the liquid that is being interchanged between the two compartments is assumed to be constant, q_2 being the urine flow, then, $c_1(t)V_1$ is the amount of substance accumulated in I at any instant, $c_2(t)V_2$ the amount accumulated at any instant in E, $[c_1(t)—c_2(t)]\ q_1$ the rate of interchange of the substance between I and E, and finally, $c_3(t)\ q_2$ is the rate of elimination. In the case under consideration, the substance (inulin) is eliminated only by glomerular filtration, and if the renal clearance at any instant is q_3, then $c_3(t)\ q_2 = c_1(t)\ q_3$. The substance will be introduced into the system in the form of a chemical solution with a rate CQ, where C is its concentration and Q is the rate of infusion, both C and Q being kept constant experimentally.

Under these conditions, the rate of accumulation of the substance in the vascular compartment will be:

$$V_1 \frac{dc_1}{dt} = QC - q_1(c_1 - c_2) - q_3c_1 \qquad (1)$$

* Dazian Foundation Fellow.

1 Gaudino, M., Schwartz, I. L., Levitt, M. F., PROC. SOC. EXP. BIOL. AND MED., 1948, **68**, 507.

2 Gaudino, M., Levitt, M. F., *Am. J. Physiol.*, 1949, in press.

† Volumes are expressed in cc of fluid, independently of any volume effects of protein, flows in cc per minute, concentrations in mg per cc.

and the rate of accumulation in the interstitial compartment:

$$V_2 \frac{dc_2}{dt} = q_1(c_1 - c_2) \qquad (2)$$

Equation (1) and (2) form a system of linear differential equations the solutions of which are:

$$c_1(t) = A\, e^{\lambda t} \qquad (3)$$

$$c_2(t) = B\, e^{\lambda t} \qquad (4)$$

Substituting (3) and (4) into (1) and (2), after appropriate differentiation:

$$V_1V_2\lambda^2 + (V_1q_1 + V_2q_1 + V_2Q_3)\lambda + q_1q_3 = 0 \qquad (5)$$

(5) being the characteristic equation corresponding to the system (1) (2). The roots λ_1 and λ_2 of (5) will be:

$$-(\lambda_1,\lambda_2) = (\beta,\alpha) \qquad (6)$$

and

$$(\beta,\alpha) = \frac{1}{2V_1V_2}\left[(V_1q_1 + V_2q_1 + V_2q_3) \pm \sqrt{(V_1q_1 + V_2q_1 + V_2q_3)^2 - 4q_1q_3V_1V_2} \right] \qquad (7)$$

Depending on the manner in which the substance is introduced in the organism, different solutions of this system of differential equations will be obtained. Three cases will be considered: (a) the substance will be introduced in the form of a rapid and single injection; (b) it will be introduced at a constant rate until uniform distribution between the intravascular and interstitial compartments has been reached; (c) the behavior of the substance will be studied after the cessation of the infusion required to maintain the steady state represented by (b).

(a) *Single injection.* In the case in which a single injection is given (50 cc in about 1 minute) the substance can be assumed to be introduced instantaneously into the system. Then, the following solution holds:

$$c_1(t) = A\, e^{-\alpha t} + B\, e^{-\beta t} \qquad (8)$$

where A and B are integration constants which are calculated from (1) and (8). Their values are:

$$A = \frac{\beta c_1(o)}{\beta - \alpha} \qquad (9)$$

$$B = -\left(\frac{\alpha c_1(o)}{\beta - \alpha}\right) \qquad (10)$$

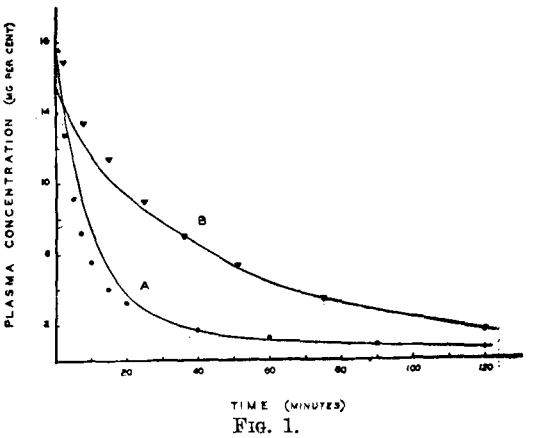

FIG. 1.

Rate of disappearance of inulin from the plasma after a single injection (A) and after a constant infusion (B). The curves are calculated from equations (8) and (17) respectively, the values $\alpha = 0.01$, $\beta = 0.10$, A = 2.0, B = 15.2, P = 12.4, R = 3.0, being obtained by trial and error. The two curves were obtained in the same dog.

$c_1(o)$ representing the concentration of the substance in I at $t = 0$.

Equation (8), with the appropriate substitutions, gives the solution of this case and permits the calculation of the rate of disappearance of the substance from the intravascular compartment.

To test this equation, single injections of inulin were given to 3 normal dogs and the plasma concentration was determined at frequent intervals and related to time. The results were identical in all of the experiments, the observed curve corresponding closely with the theoretical curve calculated by giving values to the constants in (8), (Fig. 1A).

(b) *Constant infusion.* If the rate of introduction of the substance is the same as the rate of elimination (a condition attained by constant intravenous infusion), then,

$$q_3c_1 = QC \text{ or } c_1 - \frac{QC}{q_3} = 0 \qquad (11)$$

Letting

$$c_1 - \frac{QC}{q_3} = y, \qquad (12)$$

the general solution of (5) is

$$y = K\, e^{-\alpha t} + D\, e^{-\beta t} \qquad (13)$$

and hence

$$c_1(t) = \frac{QC}{q_3} + K\, e^{-\alpha t} + D\, e^{-\beta t} \qquad (14)$$

in which α and β are defined by (7) and K and D are constants of integration with the following values:

$$K = \frac{QC - V_1\beta\left(\frac{QC}{q_3}\right)}{V_1(\beta - \alpha)} \quad (15)$$

$$D = -\frac{\left[QC - V_1\alpha\left(\frac{QC}{q_3}\right)\right]}{V_1(\beta - \alpha)} \quad (16)$$

that can be replaced in (14).

According to equation (14) when t becomes infinite the concentration of the substance in the blood will depend only on the rate of infusion and on the rate of glomerular filtration. As both are supposed to be constant, the plasma concentration also becomes constant. Further, since it was assumed that the rate of mixing of the substance in both compartments is rapid, the concentration in the interstitial space can be considered the same as the concentration in the plasma water.

Experimentally, this equilibrium has been attained in 2 hours in the dog.[2] In both cases the blood level follows the general pattern described by (17).

(c) *After cessation of constant injusion.* The general solution of (5) after a constant infusion has been discontinued is:

$$c_1(t) = P\,e^{-\alpha t} + R\,e^{\beta t} \quad (17)$$

where P and R are integration constants with the values:

$$P = \frac{\beta V_1 c_1(n) - q_3 c_1(n)}{V_1(\beta - \alpha)} \quad (18)$$

$$R = -\left(\frac{\alpha V_1 c_1(n) - q_3 c_1(n)}{V_1(\beta - \alpha)}\right) \quad (19)$$

Here $c_1(n)$ is the concentration in the plasma water at the moment of interrupting the infusion when $t = n = O$. It will be observed that the only difference between (8) and (17) lies in the values of the integration constants.

The decrement in plasma concentration in relation to time was studied in 3 normal dogs after the interruption of a constant infusion of 2 hours duration. The results obtained were similar in the three cases and again show good correspondence with the theoretical curve obtained by giving values to P and R in (17) (Fig. 1B).

The difference between the curves obtained (a) after a single injection and (b) after constant infusion to equilibrium shows that uniform distribution is never reached after a single injection.

Further, as during constant infusion, the condition stated in (11), namely that $CQ = q_3c_1$, is fulfilled at the moment of interruption the amount of substance (Z) contained in both I and E will disappear from the body at a rate expressed only by q_3c_1. The total amount of inulin excretion will then be given by:

$$Z = q_3\int_0^\infty c_1(t)\,dt \quad (20)$$

Introducing (17) with the appropriate substitution in (20), integrating within the limits indicated, and substituting the values of α and β from (7), the result is:

$$(V_1 + V_2) = \frac{Z}{c_1(n)} \quad (21)$$

where $V_1 + V_2$ is the total volume of the extracellular space. This volume can then be calculated by dividing the total amount (Z) of inulin excreted since the interruption of the infusion, by the concentration $c_1(n)$ of this substance in the blood at the moment of interruption, as previously reported.[1,2] The volume of distribution of inulin thus measured corresponds to 19 per cent of the body weight in the dog[2] and to 16 per cent in man.[1]

Summary. Comparison of the rate of disappearance of inulin from the plasma after a single injection and after prolonged constant infusion yields data which, on mathematical analysis, conform with the assumption that in the latter circumstance, inulin is uniformly distributed throughout some fixed volume of body fluid, presumably the extracellular fluid.

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