A discussion of the antagonism existing between insulin and adrenalin will not be given in this preliminary report. Adrenalin dilutions were made only at the beginning of an experiment and it is not known how much deterioration occurred. However, the rate of injection at the beginning of the experiment was within the range of epinephrine secretion found by Stewart and Rogoff[2] in blood coming from the adrenal glands (0.00015-0.001 mg. per kilo per minute). More experiments are being conducted, but our results so far seem to indicate that the hypophysectomized animals require more adrenalin to prevent convulsions following insulin than animals subjected to suppression of epinephrine secretion from the adrenals. Further, it would seem probable that the hypophysectomized animal does not liberate effective amounts of adrenalin during insulin hypoglycemia.

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Studies of Renal Excretion of Creatinine. II. Volume of Distribution.

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By studying the time change of the concentration of a substance in the plasma and of its simultaneous rate of excretion in the urine, the conclusion has been reached[1, 2] that both these quantities decrease exponentially to the pre-ingestion level and furthermore, that the coefficients of the time in both exponential functions are equal, on an average, for a given substance. From these 2 facts it follows that the rate of excretion of a substance obeying such laws is proportional to the plasma concentration at any time. The above statements have been verified so far only for creatinine and xylose.

In symbols we have

$$\eta = ae^{-\alpha t} \quad (1)$$

$$\xi = be^{-\beta t} \quad (2)$$

$$\alpha = \beta \quad (3)$$

$$\eta = A\xi \quad (4)$$

$$A = (a/b) \quad (5)$$

$$\eta = y - y_e \quad (6)$$

$$\xi = x - x_e \quad (7)$$

2 Stewart and Rogoff, *Am. J. Physiol.*, 1919, **48**, 397.

1 Dominguez, R., and Pomerene, E., *J. Biol. Chem.*, 1934, **104**, 449.

2 Dominguez, R., and Pomerene, E., *Proc. Am. Physiol. Soc.*, New York, March, 1934.

where y is the rate of excretion in mg. per minute, x the plasma concentration in mg. per 100 cc., y_e and x_e the mean pre-ingestion levels of y and x respectively, a, b, α, and β, constants determined from the experimental data, e the base of natural logarithms, and t the time in hours.

Equations 5, 6, and 7 are simply the definitions of A, η and ξ; Equations 1 and 2 are the empirical laws mentioned above; Equation 3 is an empirical fact, proved so far for creatinine and xylose, and Equation 4 is the result of the elimination of t between Equations 1 and 2.

A has been called the *excretion constant*.[1] It has the dimensions of flow $[l^3t^{-1}]$, and is measured in units of 100 cc. per minute. β has the dimension $[t^{-1}]$, and is, from Equation 2, the velocity constant of the disappearance of the substance from the body. It will be called, for the sake of brevity, the *velocity constant*.

When a substance is introduced into the blood stream a part passes out of the blood vessels and distributes itself in the tissue fluids. In the case of substances which are excreted (wholly or in part) this phenomenon is reversible, so that a state of equilibrium can be postulated. Under the assumption that equilibrium is maintained during the exponential decrease of excretion, the volume of body fluid dissolving the substance at the same concentration as the plasma, can be calculated. This volume will be called the *volume of distribution* (V), without any implication as to the actual distribution of the substance.

In order to include the case of substances such as xylose and creatinine, which are in part excreted by the kidney and in part disposed of in some other way, the calculation will proceed as follows:

Let us call Δz a small amount of substance excreted by the kidney in the time Δt, and Δu a small amount of the same substance removed from the body in the same time by any means consistent with the developments that follow. Then, evidently,

$$\Delta z + \Delta u = -\frac{V}{100}\frac{d\xi}{dt}\Delta t \qquad (8)$$

where V is the volume of distribution and ξ is, as before, the concentration of the substance. The minus sign is due to the fact that as time elapses the concentration diminishes. If the time Δt is assumed sufficiently small, Equation 8 can be written

$$\frac{dz}{dt} + \frac{du}{dt} = -\frac{V}{100}\frac{d\xi}{dt} \qquad (9)$$

Here, (dz/dt) is equal to the former η. It is, therefore, proportional to ξ (Equation 4). If we assume that (du/dt) is also proportional to ξ,

$$\frac{du}{dt} = B\xi \qquad (10)$$

where the proportionality factor B may be called *utilization constant* for lack of a better name, we have, by substituting in (9),

$$A\xi + B\xi = -\frac{V}{100}\frac{d\xi}{dt} \qquad (11)$$

The integration of this equation gives

$$\xi = ce^{-\frac{100(A+B)}{V}t} \qquad (12)$$

where c is the constant of integration.

This equation is of the same form as the empirical result symbolized in (2).

Comparison of the coefficients of t in (2) and (12) gives

$$V = 6000(A + B)/\beta \qquad (13)$$

the factor 60 arising from the fact that the rate of excretion per unit concentration (A) has been measured in minutes while the rate of change in concentration per unit concentration (β) has been determined in hours. With a suitable change in units the factor 6000 may be made to disappear. Equation 13 then signifies: *The volume of distribution of a substance is proportional to the sum of its rate of excretion plus its rate of utilization (both per unit concentration), and inversely proportional to the velocity constant of its elimination from the body.* Since, for any given subject, A, B, and β depend on the substance used, it is clearly worthless to speculate on the distribution of a substance in the body simply from a knowledge of the plasma concentration and an assumed percentage of body fluids.

Since A and B have the dimensions $[l^3t^{-1}]$ and β has the dimension $[t^{-1}]$, the right hand side of Equation 13 has the dimension $[l^3]$, as it should.

In view of the importance of the relation symbolized by Equation 13, in connection with the physiology of excretion and absorption, it should be pointed out that the hypothesis leading to this result, namely, that the utilization (or disposal) of the portion of the substance not excreted by the kidney proceeds at a rate proportional to the plasma concentration, is not only consistent with experiment, as already shown, but is the only hypothesis consistent with it. This can be proved as follows:

Let the rate of utilization be any function of ξ, say, $f(\xi)$

$$\frac{du}{dt} = f(\xi) \tag{14}$$

Then Equation 9, with the help of (4), becomes

$$A\xi + f(\xi) = -\frac{V}{100}\frac{d\xi}{dt} \tag{15}$$

But, from experiment, (2) holds, which upon differentiation with respect to t, yields,

$$\frac{d\xi}{dt} = -\beta\xi/60 \tag{16}$$

Substituting this expression for $(d\xi/dt)$ in (15) and rearranging, we obtain

$$f(\xi) = [(V\beta/6000) - A]\xi \tag{17}$$

that is, since the expression within brackets is constant for a given substance, the rate of utilization must be proportional to the plasma concentration in order to satisfy the experimental result represented by (2), which was to be proved. Substituting in (17) the value of V from (13), we see that the factor of proportionality is precisely B.

From (13) it follows that, in the case of a substance which is not destroyed in the body, ($B = 0$), the volume of distribution becomes simply

$$V = (6000A)/\beta \tag{18}$$

provided—and this is essential—that the substance is *solely and entirely* eliminated by the kidneys. This provision is necessary because in the derivation of V nothing was assumed concerning any of the various means of disposal, one of which may be excretion through another emunctory. In this case, although the substance would not be utilized in the body, Equation 18 would not apply, because B, with the meaning of another excretion constant, would not be zero.

We shall show in the following paper how the utilization constant B can be calculated.