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Studies of Renal Excretion of Creatinine. III. Utilization Constant.*

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In the preceding paper it was shown that, when a substance disappears exponentially from the body, and the rate of excretion by the kidneys is proportional to the plasma concentration, the rate of utilization of the portion not excreted is also proportional to the plasma concentration. The latter factor of proportionality was called utilization constant *(B)*, in contradistinction to the former, excretion constant *(A)*. The constant A for creatinine and xylose on one human subject has been published elsewhere. The calculation of B is as follows:

Let us call ξ_o the initial concentration at the time zero. Then the quantity initially present, M let us say, is

$$M = V\xi_o/100 = 60(A + B)\xi_o/\beta \qquad (19)^*$$

The amount excreted in the time t is, from (1),

$$\int_o^t \eta.dt = (60/\alpha)(\eta_o - \eta_t) \qquad (20)$$

the subscripts o and t meaning as usual the value of the variable at zero time and time t respectively.

The latter equation, written in terms of ξ, becomes,

$$\int_o^t \eta.dt = (60A/\alpha)(\xi_o - \xi_t) \qquad (21)$$

Therefore, since $\alpha = \beta$,

$$M - \int_o^t \eta.dt = (60/\alpha)(B\xi_o + A\xi_t) \qquad (22)$$

Since the integral in this equation has a limit, S say,

$$\int_o^\infty \eta.dt = (60A/\alpha)\xi_o = S \qquad (23)$$

we see that

$$M - S = (60/\alpha)B\xi_o \qquad (24)$$

* In order to save space the equations of this paper and the one preceding are numbered in sequence.

and consequently, that

$$(M - S)/S = (B/A) \tag{25}$$

or

$$(S/M) = A/(A + B) \tag{26}$$

An approximation to the ratios on the left side of (25) and (26) has usually been obtained experimentally by comparing an amount S' excreted in a sufficiently long interval of time to a quantity M' given orally, or to the quantity M, precisely, given intravenously. The ratio (S'/M') after oral administration would be an approximate value of (S/M) in (26) if it could be assumed that *all* the quantity given is absorbed. The ratio (S'/M) after *intravenous* injection could also be used as an approximation if it were proved that the amount excreted before the equilibrium between plasma and tissues is established, is negligible in comparison with the total amount excreted.

Lacking definite information on these points, we shall use a few figures from the literature in order to get an idea of the order of magnitude of the volume of distribution of creatinine and xylose. It should be pointed out that the "characteristic ratio" of McCance and Madders[1] is $(M—S')/S'$, where M is the quantity of pentose injected intravenously.

For creatinine, the figures for (S'/M') have rarely been higher than 0.80.[2] Our own figures for Subject E[3] yield a mean ratio (S'/M') equal to 0.73. Inasmuch as the approximation to (S/M) after oral administration is by defect, we shall take $(S/M) = 0.80$.

For xylose, the figures are very discordant, ranging, after intravenous injection, between 0.25,[4] and 0.62.[5] The mean of McCance and Madders' experiments is 0.41. We shall use this figure.

From (26), taking the above values of (S/M) and the values of A previously given for Subject E,[3, 6] namely, 1.82 for creatinine and 0.77 for xylose, we find that the utilization constant, B, of creatinine is equal to 0.46 and that of xylose 1.06, which enables us to calculate the corresponding volumes of distribution in Equation 13 of the preceding paper.

The volume of distribution of creatinine and xylose. With the

[1] McCance, R., and Madders, K., *Biochem. J.*, 1930, **24**, 795.

[2] For literature see: Hunter, A., *Physiol. Rev.*, 1922, **2**, 586.

[3] Dominguez, R., and Pomerene, E., *J. Biol. Chem.*, 1934, **104**, 449.

[4] Fishberg, E. H., and Friedfeld, L., *J. Clin. Invest.*, 1932, **11**, 501.

[5] Keith, N. M., Power, M. H., and Peterson, R. D., *Proc. Staff Meetings*, Mayo Clinic, 1934, January 17, 43.

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

assumed values of B just given, the volume of distribution, in Subject E, with a body weight of 45 kg., becomes for creatinine,

$$V = 6000(1.82 + 0.46)/0.29 = 47.2 \times 10^3 \text{ cc.},$$

and for xylose,

$$V = 6000(0.77 + 1.06)/0.5756 = 19.1 \times 10^3 \text{ cc.}$$

Seeing that the volume of distribution of creatinine, if considered as water, is equivalent to the weight of the whole body, it is at once evident that there must be condensation of creatinine in the tissues, whether creatinine is uniformly distributed or not.

The large volume of distribution of creatinine clears up some of the difficulties of Heesch and Tscherning,[7] who, after stating that the excretion of creatinine is less dependent on renal activity than the excretion of phenolsulphonphthalein, say, "Vielmehr spielen die Gewebe hier die fast Ausschlaggebende Rolle; die Rückwanderung aus ihnen bestimmt das Tempo der Ausscheidung, ohne das Blut and Niere erkennbar an der Ausscheidung Anteil nehmen." If we should inject 500 mg. of creatinine intravenously in Subject E, and assume equilibrium to be reached so soon after injection that the amount excreted during this time can be neglected in comparison with the whole amount excreted, the initial concentration at equilibrium would be $500/376 = 1.33$ mg. per 100 cc., and the concentration at the end of an hour (the duration of the interval in Heesch and Tscherning's experiments), 0.995 (from Equation 2 and $\alpha = 0.29$). The amount excreted in an hour would be, from (21), 126 mg. plus the endogenous amount (60×0.724), namely, 169 mg. of creatinine, a quantity which corresponds to a fall in plasma concentration from 2.37 (1.33 plus the endogenous blank, 1.04) to 2.04 (0.995 plus the endogenous blank). That is to say, on account of the small quantity injected and the large volume of distribution of creatinine, the changes in concentration are not recognizable because they lie within the province of the experimental error.

Whether the rate of the fall of plasma concentration is due mostly to the release of creatinine from the tissues and to a lesser degree to the excretory ability of the kidney, the experiments of Heesch and Tscherning are insufficient to determine. Yet, if creatinine is so readily taken up by the tissues and the process is reversible, there is no *a priori* reason why the tissues should not give it off just as readily, in which case the *tempo* of the excretion will be determined by the excretory activity of the kidneys, the tissues acting only as a reservoir so to speak.

[7] Heesch, O., and Tscherning, R., *Z. f. Klin. Med.*, 1920, **104**, 277.

From (21) we see also that when the plasma concentration of creatinine is 20 mg. per 100 cc. the amount of creatinine in Subject E is at least (B assumed equal to zero) $(60 \times 1.82 \times 20)/0.29 = 7531$ mg., while with the same plasma concentration the amount of xylose in the body would be (B assumed equal to 0.46) $(60 \times (0.77 + 0.46) \times 20)/0.5756 = 3815$ mg. Since (under the assumptions concerning the values of B) the entire quantity of creatinine is to be excreted by the kidneys, but only about 41% of the amount of xylose, the behavior of these 2 substances as illustrated elsewhere (Fig. 1)[8] becomes easily understandable.

This fact also accounts for the large value of the excretion constant of pentoses as estimated by McCance and Madders.[1] Having no way to compute the volume of distribution, these authors assumed a volume much too large (60% of the body weight instead of 42%), and as a result the excretion constant (which they called "glomerular filtrate" after Rehberg) came out about as large as that of creatinine.

Application to the excretion constants. With the help of (9) and (11), we can write

$$\frac{dz}{dt} + \frac{du}{dt} = C\xi \tag{27}$$

where C is equal to $(A + B)$. This equation may be looked upon as the completed relation connecting the concentration of the substance in the plasma with the two processes (excretion and utilization) whose simultaneous transaction leads to the eventual elimination of the substance.

Equation 27 can be written

$$\frac{d(z + u)}{dt} = C\xi \tag{28}$$

or, introducing the symbol w for the total amount disposed of,

$$\frac{dw}{dt} = C\xi \tag{29}$$

In this equation the rate of excretion and the rate of utilization are merged into one rate of disposal, and the question which immediately arises is, would C remain constant under varying states of utilization? In other words, if B can be varied, would the equation $A + B = C$ hold, with a constant value of C. If this were the case A would vary in the opposite direction, which would amount to a new definition of renal threshold. The interesting observation

[8] Dominguez, R., and Pomerene, E., *J. Clin. Invest.*, in press.

of Shannon, Jolliffe and Smith[9] that, in the dog, a change in the diet alters the value of A, would be easily accounted for by the above hypothesis. As a matter of fact, since the case of xylose is only a particular instance of the general utilization of sugar, we see that when the coefficient of utilization of glucose is large, as in normal people, the value of A is practically zero, but when the utilization of glucose diminishes, as in diabetes, the value of A becomes positive and quite large.

The excretion constant, being subordinated to the more general phenomenon of disposal, in a large sense, loses part of its significance in renal physiology in the case of substances which, like creatinine and xylose, are in part utilized in the body and in part excreted.

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A Case of Myeloid Leukemia Treated with Luminal and Amidopyrine.

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On September 15, 1933, a male negro 37 years old was admitted to the medical service with the diagnosis of myeloid leukemia. His leucocyte count was 267,000 per cu. mm. and his spleen came to the level of the umbilicus.

Four treatments by splenic irradiation in doses of 145 r, beginning October 6, brought the count down to 156,000. This effect was transitory; on November 21 the count was 269,000 and there was no reduction in the size of the spleen.

From November 21 to March 7, 1934, the patient was given subcutaneous injections of his own leucocytes, each injection consisting of the cells recovered from 10 cc. of his blood taken in citrated salt solution the day before injection. This treatment, based on an encouraging report by Lindstrom[1] and previously used by one of us (M.C.T.) with apparent benefit in 2 unpublished cases, was without avail in the case here reported, the count continuing to rise until, on March 7, it was 500,000 with the spleen as large as before.

Beginning March 8 four small doses of X-ray irradiation (72 r)

[9] Shannon, J. A., Jolliffe, N., and Smith, H., *Am. J. Physiol.*, 1932, **101**, 625.

[1] Lindstrom, G., *Arch. du mal du coeur*, 1921, **14**, 145.