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Some Factors Governing Renal Function.

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With the ultimate objective of finding a satisfactory method for the quantitative demonstration of impairment of renal function in humans, the authors have studied the rate of elimination of urea, as compared with the amount of urea in the blood and with the simultaneous excretion of water. The previous work of Ambard,[1] McLean,[2] and Addis,[3] and of the associates and critics of these experimenters, has been considered in detail.

In regard to the relationship of blood urea levels to rate of urea excretion, it will be recalled that there are two divergent schools of thought. The older group, of which Ambard and McLean are the outstanding examples, have shown that the rate of excretion is a parabolic function of the concentration of urea in the blood, according to the equation $Ur = K\sqrt{D}$. Ur = Gm. urea per liter blood. D = Gm. urea per 24 hr. (Measured over a short period and extrapolated for the 24 hours.) Addis, and later Adolph,[4] on the other hand, under conditions involving a large provocative ingestion of either urea of water, or both, have demonstrated a linear relationship, $Ur = KD$. Under ordinary conditions, however, the relationship approaches, but does not equal, the parabolic relationship proposed by Ambard.

By combining our own data with the normal cases reported by McLean and by Addis (excluding the cases where provocative doses had been given) we were able to calculate this relationship in 220 normal individuals. By simultaneous determination of the Pearson correlation coefficient, the correlation ratios and comparison of

these with each other and with the probable error, according to the method of Blakeman,[5] it was possible to demonstrate that the relationship in these normal cases was not linear. By taking the averages of all values of D for each value of Ur and plotting them logarithmically against the values of Ur, a curve is obtained, the equation of which is $Ur = .0340(D)^{.72379}$. This defines a sub-parabola, lying intermediate between the parabola of Ambard and the line of Addis.

Over the range of the values of blood urea usually found in normals and in nephritics (exclusive of the late stages of uremia) this relationship varies from that proposed by Ambard (taking a constant of 0.08) by less than the ordinary variations of either. Assuming a constant of 0.10 in the Ambard equation defines a limit dividing the values found in normals, or incipient nephritics, from those found in the more advanced stages of the disease. This curve includes 96.5 per cent of the normal cases. A similar limiting curve drawn on a basis of the Ambard equation, with a constant of 0.075, gives us a basis of division between the nephritics of all grades and the normal, and includes 96 per cent of all the nephritic cases studied. The area intermediate to these two curves is an indeterminate area, with a suspicion of pathology.

To simplify calculation, we have altered the original Ambard formula by inverting it and adding a coefficient 7.5, which permits us to group our subjects on the scale of 100, in accordance with the McLean convention. This final form of the Ambard expression is $7.5\sqrt{D/Ur} = F$—functional capacity of kidney on scale of 100. The following table gives a summary of the distribution of our cases on this basis:

	Normal Cases	Cases with Renal Impairment
F above 100 (high normal group)	76%	4%
F between 100 and 75 (low normal or doubtful group)	20.5%	56%
F below 75 (deficient group)	3.5%	40%

It will be patent to the observer that this formula is a simplified form of the well-known McLean index, with the factors for body weight and urine concentration omitted. These two factors, and especially the latter, we have found not only to add nothing to the validity of the determination, but in many cases to lead to false results, especially in normals. The urine concentration factor in

the McLean index is based upon the second law of Ambard, which may be expressed $D/D' = \sqrt{C'}/\sqrt{C}$ when Ur is constant and C is the grams urea per liter urine. This relationship has been investigated by Addis and by us, and found to be entirely unreliable. In repeated investigations upon the same individual, where Ur was the same, the two ratios differed from each other by values up to 360 per cent.

This leads to the consideration of the nature of the relationship between variations in urine volume and urea output. Taking the same 220 cases, from which were derived the blood urea-output relationship, together with the averages of output for each value of urine volume, it is found that up to the rate of volume output of 100 cc. per hour the urea output increases as a linear function of the volume output, the equation being roughly $D = V/2$ where V = cc. urine per hour. Above this limit the relationship becomes obscured by other factors. This "augmentation limit" phenomenon has been previously demonstrated by Austin, Stillman and Van Slyke,[6] and confirmed by Rabinowitch.[7]

The most reasonable explanation of this partial correlation is, we believe, that proposed by Crawford and McKintosh.[8] When there is no excess of water to be eliminated, the elimination of water is determined by the amount of solutes to be excreted, a condition in which urea would be a major factor. Hence for each blood urea level there would exist a definite volume for the excretion of urea. In the presence of excess water, however, there would be an elimination of water regardless of the amount of urea simultaneously excreted, and there would be no quantitative relationship.

In case this is the true state of affairs, it becomes evident that the inclusion of a volume correction in the ratio for the expression of functional capacity is unnecessary and inadvisable, since, statistically speaking there is a determined volume for the excretion of urea at each blood urea level. In individual cases there is wide variation from this statistical mean, but these variations have not been shown to be functionally diagnostic.

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[2] McLean, *Am. J. Physiol.*, 1915, xxxvi, 357; *J. Exp. Med.*, 1915, xxii, 212; *J. Exp. Med.*, 1915, xxii, 366.

[3] Addis, T., *J. Biol. Chem.*, 1917, xxviii, 251; *J. Biol. Chem.*, 1917, xxix, 391; *J. Biol. Chem.*, 1917, xxix, 399; *Arch. Int. Med.*, 1922, xxx, 377. Addis and Drury, *J. Biol. Chem.*, 1923, lv, 105; *J. Biol. Chem.*, 1923, lv, 629. Addis and

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[4] Adolph, *Am. J. Physiol.*, 1925, lxxiv, 93.

[5] Blakeman, *Biometrika*, 1906, iv, 332.

[6] Austin, Stillman, and Van Slyke, *J. Biol. Chem.*, 1921, xlvi, 91.

[7] Rabinowitch, *J. Biol. Chem.*, 1925, lxv, 617.

[8] Crawford and McKintosh, *Arch. Int. Med.*, 1925, xxxvi, 530.

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Galvanotropism and "Reversal of Inhibition" by Strychnine.

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Definite neuromuscular effects are produced in a variety of organisms by the passage of a constant electric current. The character of the induced galvanotropic curvatures and movements has played a certain part in the development of the tropism doctrine (*cf.* Loeb, 1918), but these reactions still await quantitation, which is difficult, as well as fuller utilization for the analysis of animal movements. The interpretation of galvanotropism in metazoans turns upon the at present necessary and sufficient assumption that the current serves to excite definite groups of nerve cell bodies (presumably as determined by the axial orientation of these cells with respect to the polarity of the current.[1, 2, 3] The effects are such that among annelids, for example, the animal typically extends and lengthens when the head is toward the cathode, but shortens when the current is in reverse direction. These effects are in certain respects similar to those produced by neurophil drugs. Strychnine, for example, induces a similar and comparable elongation, whereas nicotine leads to shortening. It was considered that if the effects of such alkaloids are indeed due to selective or differential unions with particular groups of nervous elements, the result of combining the action of a substance of this type with that of the electric current should be merely an accentuation of the primary action, since the response induced involves activity of the same nerve muscle groups. In certain cases this turns out to be true.

The effect of strychnine is of especial interest. In the spinal cord of vertebrates it is usually supposed that the strychnine effect is due to abolition of the inhibitory component of normal coördination, so that the inhibitory effect is transposed into an excitatory one.