

## Excretion of Urea and Creatinine in the Dog in Relation to Rate of Urine Formation.

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Austin, Stillman and Van Slyke<sup>1</sup> on the basis of data obtained on a series of normal men, showed that when the urine flow was progressively increased from very low values the urea clearance also increased until the rate of urine excretion reached a value they termed the augmentation limit. At rates of urine excretion above the augmentation limit there was found to be no further increase in urea clearance. Subsequently this description has been accepted for dogs by Jolliffe and Smith<sup>2</sup> and Summerville, Hanzel and Goldblatt,<sup>3</sup> and it has been tacitly assumed by Van Slyke, Rhoads, Hiller and Alving<sup>4</sup> in their study of factors controlling urea excretion. A maximum urea clearance has also been posited by Dominguez<sup>5</sup> in his mathematical treatment of the relation existing between urea clearance and urine flow at rates of urine formation below the augmentation limit. The value fixed for the augmentation limit in the dog has been variously stated to be from 0.2 to 0.4 cc. per minute, depending in part upon the size of the animal, and also upon the level of the maximum clearance, which can be varied by changing protein intake.

Recent evidence has made it possible to accept the creatinine clearance as a measure of the rate of glomerular filtration in the dog. (Shannon,<sup>6</sup> Van Slyke, Hiller and Miller<sup>7</sup>), even at very high U/P ratios (Shannon<sup>8</sup>). The present observations were made to examine the relations between the rate of glomerular filtration and the rate of excretion of water, and the effect of these variables upon the urea clearance.

There is no standard of reference by which the clearances of

<sup>1</sup> Austin, J. H., Stillman, E., and Van Slyke, D. D., *J. Biol. Chem.*, 1921, **46**, 91.

<sup>2</sup> Jolliffe, N., and Smith, H. W., *Am. J. Physiol.*, 1931, **98**, 572; **99**, 101.

<sup>3</sup> Summerville, W. W., Hanzal, R. F., and Goldblatt, H., *Am. J. Physiol.*, 1932, **102**, 1.

<sup>4</sup> Van Slyke, D. D., Rhoads, C. P., Hiller, A., and Alving, A. S., *Am. J. Physiol.*, 1934, **109**, 336.

<sup>5</sup> Dominguez, R., *Am. J. Physiol.*, 1935, **112**, 529.

<sup>6</sup> Shannon, J. A., *Am. J. Physiol.*, 1935, **112**, 405.

<sup>7</sup> Van Slyke, D. D., Hiller, A., and Miller, B., *Am. J. Physiol.*, 1935, **113**, 611.

<sup>8</sup> Shannon, J. A., *Am. J. Physiol.*, 1936, **114**, 362.

various individual dogs can be converted to a common value. For this reason it was apparent beforehand that the data from each dog should be treated separately. We have taken cognizance of the fact that abstinence from water may change the physiological state of the animal, and consequently no experiment has been accepted that does not include a fair representation of urine flows over the entire physiological range. The experiments were conducted so that the rate of water excretion should return at some time during the observations as near to the initial state as possible; we believe that failure to observe these conditions is in part responsible for a misinterpretation of the true relation between rate of water excretion and urea clearance.

To date we have examined the urea and creatinine clearances in 405 periods in 5 dogs. Three of these dogs were observed upon a cracker meal, sucrose and lard maintenance diet, one upon a mixed diet, and one on both these diets at different times. Adequate vitamins were given to all animals and a salt mixture was used to supplement the low protein diet.

TABLE I.

Urea and creatinine clearances of Dog C., on mixed diet for 2 months prior to experiment. 1000 cc. of water were given at termination of period 2 and 500 cc. at termination of period 9. Creatinine was given 4 times in doses of 100, 50, 50 and 50 mg. per kilo. The presence of creatinine causes no change in the absolute urea clearance in relation to urine flow.

Period No.	Duration min.	Urine Flow cc. per min.	—Plasma Level—		—Clearance—		Ratio Urea Clearance Creat. Clearance
			Urea mg. %	Creatinine mg. %	Urea cc. per min.	Creatinine cc. per min.	
1	36	.191	39.4	9.52	29.2	95	.307
2	34	.20	38.5	9.26	27.8	98	.285
			1 hr. 35 min. between periods				
3	31	7.23	30.6	8.52	70.3	123.5	.570
4	31	5.42	28.6	8.15	65.5	117.6	.557
5	31	1.71	26.7	7.62	54.0	107.8	.501
6	37.5	.613	25.4	—	41.6	—	—
7	34.5	.275	24.2	9.17	38.6	111.0	.348
8	41	.268	24.0	9.52	36.8	110.6	.333
9	42	.191	23.9	8.52	26.8	101.2	.265
			1 hr. between periods				
10	30	2.40	21.1	9.31	52.8	110	.480
11	30	.933	20.1	9.20	45.4	108.2	.420
12	30	.533	19.1	8.95	39.9	108	.369

A typical experiment on one of the dogs is given in Table I. It is apparent that in this animal there is no point on the urea curve that can be designated as an "augmentation limit", in the sense of Austin, Stillman and Van Slyke.<sup>1</sup> There is a systematic increase in urea clearance with increasing urine flow throughout the entire range

of the latter. This increase in urea clearance is in part due to an increase in the amount of urea filtered (creatinine clearance) and in part due to diminished reabsorption of urea. In no 2 dogs that we have studied have either of these 2 factors been quantitatively the same. And in only one out of the 5 has the gross change in these 2 variables—rate of filtration and reabsorption of urea—been quantitatively so small as to produce an approximately constant urea clearance above 0.5 cc. per minute.

It may be noted that in any instance where the urea-creatinine clearance ratio changes with changing urine flow, the extraction ratio of both substances could not in theory be constant and independent of urine flow.

The theoretical treatment of urea clearances below the augmentation limit as proposed for the dog by Dominguez loses its significance in view of the fact that in many, and possibly most dogs there is no point that can be designated as the augmentation limit.

There is little or no change in the creatinine clearance in any dog in the ordinary experimental range of urine flows (between 0.5 cc. and 3 cc. per minute). At flows lower than 0.5 cc. per minute the clearance of this substance may or may not fall, depending apparently upon the degree of dehydration of the animal. The point at which this fall takes place is below 0.2 cc. per minute in 4 out of the 5 dogs studied, and is not reproducible in any one. We were unable consistently to obtain urine flows below 0.1 cc. per minute, due perhaps to the presence of large quantities of creatinine in the urine. In some experiments this rate of urine flow was reached with no fall in creatinine clearance. The irregular decrease in glomerular filtration may arise from the conditions of our experiments, since more dehydration is necessary to obtain low urine flows in the presence of creatinine than in its absence.