procedures would have been required, conditions not compatible with objectives in these preliminary experiments.

In spite of the exploratory nature of these tentative trials, it is apparent that the life expectancy of these lizards, when under normal thermal conditions—that is, 31-38°C—is less than 2 days; whereas with moderate cooling to 27-28°C or chilling to 10-11°C, there is a material prolongation of life, in the former case by 7 to 8 days, and in the latter as much as 14 days. Unfortunately, controls were not run to determine how long a normal lizard would survive at this temperature (ice box).

Although these results might have been predicted by the use of Van't Hoffs Law, the ameliorating effects are greater than the Q_{10} of 2, and approach those of 3 to 4. This larger factor may be due to inherent differences of tissues or to physiological functions, but at present it seems more probable that the explanation may lie in the realm of normal differences of the Q_{10} for different thermal levels.

Conclusions. 1. Contrary to reports indicating that "cold blooded" creatures are not susceptible to tetanus toxin, the desert iguana is susceptible and for temperature studies is an excellent experimental animal. 2. Lowering of temperature markedly prolongs life in the desert iguana inoculated with tetanus toxin. From Van't Hoffs Law one would expect a slowing down of the effects of the toxin at lower temperatures. 3. There is a tremendous field awaiting study on the effects of altering bodily temperature on the course of disease, especially where toxic factors are concerned.

15751

Use of Thiosulfate Clearance As a Measure of Glomerular Filtration Rate in Acidotic Dogs.*

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The renal clearance of thiosulfate has recently been proposed as a measure of glomerular filtration rate in the normal dog[1] and in man.[2] Since the majority of the ionic constituents of the glomerular filtrate are more or less completely reabsorbed during their passage through the renal tubules, the apparent tubular rejection of this anion constitutes an interesting anomaly. The present study of the excretion of thiosulfate in the acidotic dog was undertaken with the following 2 ends in view. If thiosulfate were to undergo no reabsorption in the tubules of animals with disturbed acid base relationships, as is apparently true in normal animals, that fact would strengthen the concept that its clearance constitutes an adequate and broadly applicable measure of filtration rate. If the thiosulfate clearance could be used as a measure of filtration rate in acidotic animals, it would have the following advantage over the creatinine clearance. Thiosulfate, unlike creatinine, is devoid of buffer properties. Hence, it can be predicted that the administration of this substance would not affect the rate of excretion of titratable acid, as does the administration of creatinine.[3]

In this study it has been found: (1) that the thiosulfate clearance provides an accurate means of quantitating glomerular function in

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1 Gilman, A., Philips, F. S., and Koelle, E., *Am. J. Physiol.*, 1946, **146**, 348.

2 Newman, E. V., Gilman, A., and Philips, F. S., *Bull. Johns Hopkins Hosp.*, 1946, **79**, 229.

3 Pitts, R. F., and Alexander, R. S., *Am. J. Physiol.*, 1945, **144**, 239.

acidotic dogs; (2) that the administration of thiosulfate *per se* does not significantly disturb either glomerular filtration rate or renal plasma flow; and (3) that the administration of thiosulfate does not greatly alter the rate of excretion of titratable acid. Accordingly, the thiosulfate clearance is to be preferred to the creatinine clearance in studies on renal function in animals in acidosis.

Methods. A total of 12 experiments were performed on 3 trained female dogs rendered acidotic by the oral administration of ammonium chloride. Solutions containing creatinine, sodium thiosulfate and sodium *p*-aminohippurate were infused at a constant rate into the saphenous vein. Except in Experiments 1 and 2 the rate of infusion was maintained at 3 cc per minute. In these initial experiments infusion rates of 10 cc per minute gave evidence of expansion of circulating blood volume and increased filtration rate. High infusion rates were therefore discontinued. Plasma and urine thiosulfate concentrations were determined by the plasma method of Newman *et al.*[2] Corrections were made for both plasma and urine blanks. Other procedures and chemical methods have been described in previous communications.[3,4]

Identity of the creatinine and thiosulfate clearances in acidotic dogs. In 50 comparisons of simultaneously determined thiosulfate and creatinine clearances in 3 acidotic dogs, the mean thiosulfate/creatinine clearance ratio was 1.004. In 10 experiments the ratios varied within limits of 0.95 and 1.05. In 2 experiments ratios as low as 0.90 and as high at 1.13 were observed. It is evident within limits of experimental error that the thiosulfate and creatinine clearances are equal in acidotic dogs as they are in normal dogs.[1]

In Table I are presented 2 illustrative experiments in which the plasma concentration of thiosulfate was varied from 17.8 to 55.6 mg %. The plasma concentration of creatinine was maintained essentially constant at an optimum level for the determination of filtration rate. It is obvious that the 2 clear-

TABLE I.
Comparisons of the Thiosulfate and Creatinine Clearances in the Acidotic Dog Over a Range of Plasma Thiosulfate Concentrations.

			Arterial plasma concentration				Urine		Rate of excretion		Clearance		
Exp. No.	Dog No.	Total concurrent time, min.	pH	Bicarbonate, mM/l	Creatinine, mg%	Thiosulfate, mg%	Flow, cc/min.	pH	Titratable acid, mEq./min.	Ammonia, mEq./min.	Creatinine, cc/min.	Thiosulfate, cc/min.	Ratio, Thio./Cr.
1	1	80-90	7.31	13.6	27.8	19.5	2.0	5.05	0.065	0.062	64.0	61.7	0.96
		90-100			26.3	18.3	2.0	5.01	0.074	0.071	74.3	72.8	0.98
		115-125	7.31	13.9	25.5	35.3	10.9	5.00	0.079	0.075	80.4	82.8	1.03
		125-135			25.3	34.7	10.2	5.09	0.070	0.071	79.5	79.8	1.01
		150-160	7.33	13.9	25.6	52.0	11.9	5.34	0.053	0.069	81.3	82.5	1.02
		160-170			26.4	51.1	11.9	5.32	0.054	0.069	80.8	83.4	1.03
2	2	110-120	7.29	11.0	27.4	18.6	5.6	5.10	0.060	0.085	61.3	60.2	0.98
		120-130			26.6	17.8	7.5	5.06	0.063	0.087	63.9	61.6	0.97
		150-160	7.29	11.7	27.4	36.1	11.3	5.17	0.061	0.083	68.8	71.1	1.03
		160-170			28.0	35.9	8.6	5.17	0.060	0.081	67.0	68.7	1.03
		185-195	7.31	11.6	28.9	54.8	8.0	5.24	0.057	0.085	66.1	69.0	1.04
		195-205			29.1	55.6	7.8	5.27	0.053	0.083	65.5	65.8	1.00

4 Pitts, R. F., and Lotspeich, W. D., *Am. J. Physiol.*, 1946, **147**, 138.

TABLE II.

Experiments Illustrating the Lack of Effect of the Administration of Thiosulfate on Glomerular Filtration Rate and Minimum Effective Renal Plasma Flow in the Acidotic Dog.

Exp. No.	Dog No.	Total concurrent time, min.	Arterial plasma conc. pH	Arterial plasma conc. Bicarbonate, mM/l	Arterial plasma conc. Creatinine, mg%	Arterial plasma conc. Thiosulfate, mg%	Arterial plasma conc. p-Amino hippurate, mg%	Urine Flow, cc/min.	Urine pH	Rate of excretion Titratable acid, mEq./min.	Rate of excretion Ammonia, mEq./min.	Clearance Creatinine, cc/min.	Clearance Thio. sulfate, cc/min.	Clearance p-Amino hippurate, cc/min.	Clearance ratio Thio./Cr.	Clearance ratio Cr./P.A.H.	Clearance ratio Thio./P.A.H.
3	1	110-120			29.9		1.05	2.6	5.31	.048	.077	74.4		248		.30	
		120-130	7.20	9.8	29.4		1.12	2.4	5.26	.050	.075	71.1		234		.30	
		130-140			30.2		1.19	2.1	5.19	.050	.081	74.1		238		.31	
		170-180			30.6	51.5	1.38	2.0	4.99	.090	.079	75.4	74.0	238	.98	.32	.31
		180-190	7.22	10.0	30.5	51.3	1.29	2.5	4.98	.098	.079	78.9	77.6	265	.98	.30	.29
		190-200			30.6	52.4	1.22	2.4	4.99	.088	.076	78.9	75.2	268	.95	.30	.28
4	1	115-125			23.7		1.69	2.9	5.72	.021	.069	74.2		234		.32	
		125-135	7.33	14.5	23.8		1.69	5.4	6.10	.010	.055	71.6		217		.33	
		135-145			24.0		1.69	6.5	6.26	.008	.048	74.8		221		.34	
		165-175			24.5	28.2	1.75	2.9	5.00	.064	.074	68.3	66.2	197	.97	.35	.34
		175-185	7.36	15.1	25.1	25.9	1.73	1.5	4.92	.070	.076	68.1	66.7	198	.98	.34	.34
		185-195			25.1	24.9	1.68	1.2	4.86	.082	.078	73.2	71.0	217	.97	.34	.33
5	1	100-110				41.9	1.63	3.8	5.37	.006	.092		77.1	228			.34
		110-120	7.27	11.4		42.4	1.72	2.0	5.25	.005	.093		71.3	208			.34
		120-130				41.7	1.70	1.3	4.84	.007	.094		74.0	219			.34
		150-160			36.3	39.7	1.59	8.0	5.08	.087	.085	76.5	72.9	232	.95	.33	.31
		160-170	7.27	11.6	35.9	38.9	1.58	10.9	4.95	.106	.084	78.4	77.8	233	.99	.34	.33
		170-180			36.5	38.7	1.58	5.2	5.08	.088	.080	81.0	78.6	232	.97	.35	.34
6	1	90-100				41.7	1.46	7.5	4.71	.008	.076		71.8	219			.33
		100-110	7.29	14.6		39.8	1.46	3.6	4.84	.008	.074		70.4	215			.33
		110-120				38.7	1.47	1.6	4.69	.008	.074		65.9	195			.34
		120-130			27.9	37.8	1.62	1.9	4.92	.085	.078	73.5	74.1	213	1.01	.35	.35
		130-140	7.29	14.4	28.3	37.6	1.61	4.3	4.88	.088	.078	70.7	71.9	214	1.02	.33	.34
		140-150			28.9	38.4	1.62	4.7	4.87	.094	.076	73.9	73.5	213	1.01	.35	.35

ances are in essential agreement, and that the thiosulfate clearance is independent of plasma level over a 3-fold range of concentration. For these reasons we feel that the thiosulfate clearance gives as accurate an estimate of the quantity of fluid filtered through the glomeruli as does the creatinine clearance. The severity of the acidosis in the animals used in these experiments is indicated both by the low arterial pH values, and by the reduced plasma bicarbonate concentrations. As a consequence of the acidosis the urines were highly acid and ammonia and titratable acid were excreted at accelerated rates. It is significant that the buffering capacity of the urinary creatinine accounts for over 90% of the titratable acid eliminated.

Lack of effect of thiosulfate on glomerular filtration rate and minimum effective renal plasma flow. It is apparent from Experiments 3 and 4 in Table II, that the administration of thiosulfate is without significant effect on filtration rate and minimum effective renal plasma flow. Throughout both experiments these renal variables were measured respectively by the creatinine clearance and by the *p*-aminohippurate clearance. The initial 3 periods of each experiment constitute the control observations. During the final 3 periods thiosulfate was infused at such a rate that its clearance could be used as an accurate measure of filtration rate. No really significant change occurred in either filtration rate or renal plasma flow as a result of the infusion of thiosulfate, slight increases in Experiment 3 being offset by slight decreases in Experiment 4. Identical experiments on 2 other animals yielded similar results.

Advantage of thiosulfate over creatinine in experiments in which titratable acid is to be measured. It was noted in connection with Experiments 1 and 2 that over 90% of the observed urinary titratable acid could be ascribed to the buffering action of creatinine. Experiments 5 and 6 emphasize the fact that the administration of creatinine very markedly increases the rate of elimination of titratable acid in the acidotic animal. In the initial 3 periods of each experiment little buffer substance was present in the urine, and as a consequence the rate of excretion of titratable acid was low, amounting only to 0.005 to 0.008 milliequivalents per minute. Following the administration of creatinine the rate of excretion of titratable acid increased more than 10 times to values ranging from 0.085 to 0.103 milliequivalents per minute. Since the urinary pH did not change, the increased elimination of titratable acid derived solely from the increased elimination of creatinine.

Experiments 3 and 4 in Table II illustrate an interesting phenomenon which we have occasionally observed, namely, that the urine may not be especially acid even though the extent of the reduction of the alkali reserve is great (see especially Experiment 4). The excretion of titratable acid was moderate in this experiment although the urine contained much buffer. Following the administration of thiosulfate, the urine pH fell and the excretion of titratable acid increased proportionally. This effect on urine pH is not peculiar to thiosulfate for we have observed it following the administration of sodium phosphate, sodium *p*-aminohippurate and even sodium chloride in the dog. At the moment we have no adequate explanation for it. It is by no means universally observed.

Summary and Conclusions. The data presented above confirm the observations of Gilman *et al.*[1] that the thiosulfate clearance may be used as a valid measure of glomerular filtration rate in the dog, and extend these observations by showing that it is applicable to animals with disturbed acid base relationships as well as to normal animals. Because the administration of thiosulfate has no significant effect on glomerular filtration rate (creatinine clearance) and minimum effective renal plasma flow (*p*-aminohippurate clearance) the thiosulfate clearance may be used in studies on renal function in acidotic animals with minimal disturbance of these discrete renal variables. Since thiosulfate is not a buffer, the administration of this substance does not greatly alter the rate of excretion of titratable acid. This virtue is likewise possessed by mannitol and inulin, but the simplicity and accuracy of the thiosulfate analysis argues strongly in its favor.